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DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America. New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL
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ORIGINAL ARTICLES

AN EVALUATION OF VARIOUS EXAMINATIONS PERFORMED ON SEROUS FLUIDS*

By SPENCER K. PHILLIPS, M. D.,
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(From the Mayo Clinic)

For many years it has been possible to make a diagnosis of the disease underlying abnormal collections of fluid in the serous cavities in certain cases. However, many times serous effusions occur and it is impossible to make more than an unsatisfactory, indefinite diagnosis in the absence of convincing evidence pointing in one direction. It was with the hope of adding to the knowledge which might be derived from the examination of serous fluids that this study was undertaken, even though the evidence so derived could hardly be more than presumptive.

Review of the Literature: The first report located in which anyone found malignant cells anywhere other than in tissues was by Beale,[2] who recognized a clump of malignant cells in the sputum of a patient who had carcinoma of the pharynx. Later other clinicians [9,44,45] found malignant cells by examining stained smears of pleural and ascitic fluid. Bahrenberg[1] described a technic for embedding the sediments from centrifuged fluids and sectioning them for examination. In 1900, Mandelbaum[30] was able to diagnose actinomycosis by fixing pus in formalin, embedding it in celloidin and demonstrating the Actinomyces microsopically. Steiner[50] used the technic described by Mandelbaum to demonstrate malignant cells in effusions. This technic with minor variations still is used by some but it has been supplanted [6,10,29,32,49,51,54,58] in most cases by a different technic in which the specimen is embedded in paraffin for section as described by the same author[31] at a later date. A method of making frozen sections of the sediment fixed in formalin without the use of paraffin was described by Venable[54];

*Abridgment of thesis submitted by Dr. Phillips to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

by this method he was able to obtain good material for examination. Some authors[11,56] have stressed that paraffin sections are greatly superior to stained smears in examining sediments of serous effusions, but the results of those[28] who used smears seem to compare favorably with the results of those who used sections.

The presence of mitotic figures in the cells of effusions has been discussed by many writers, but there has been considerable disagreement as to the amount of dependence which may be placed on the finding of them in diagnosis. It has been reported[20,57] that mitotic figures have been found in the benign cells of effusions, but many authors [12,15,16,28,36,55] consider them presumptive evidence of malignancy. Evidence of atypical mitosis generally has been found only in malignant cells.[12,58]

It is generally agreed that the observation of indefinite clumping of the cells or formation of sheets is of little if any value in diagnosis of malignant disease,[12,13,28] but that the finding of definite organoid arrangement of the cells, such as the formation of acini, contributes positive evidence and makes a high degree of accuracy in diagnosis possible.[11-13,15,16,19,28,58] Some[36,48] have said that the diagnosis can be made when such formations are found but the absence of the organoid arrangement does not necessarily rule out the presence of the disease.

Multinucleation and formation of giant cells have been discussed by several authors,[12,13,15,16,35,58] but none considered them of great importance except when the giant cells are of the tumor type.

Nearly all of the writers on the subject have recognized some finer differences between the individual characteristics of the malignant cell and those of the normal cell and attached more or less importance to these differences in diagnosis. Large, deep-staining cells with large nuclei have been considered as suggestive of malignancy,[12,13,28,58] and some authors [12,17,20–28,38,42,43,57] have stressed the importance of an increase in the relative size of the nucleolus as compared with that of the nucleus. Many[12,28,49] have warned against designating as malignant the highly atypical cells found in fluids which have been present a long time while others[13,58] have considered eccentricity of the nucleus to be of diagnostic assistance.

All writers have emphasized that diagnosis of malignant disease based on examination of serous effusions carries a high degree of accuracy, but negative findings are of less importance. Nearly all report[3,19,36,49,58] that the diagnosis of malignant disease was made correctly on the basis of this examination in from 50 to 80% of their cases. In from 3 to 5% the results were erroneously positive.

Most investigators[3,34,41] of the subject have reported that the finding of various blood elements in serous effusions is of little aid in diagnosis. Norris and Landis[39] believed that a predominance of lymphocytes in pleural effusions is very suggestive of tuberculosis. Several[3,39,52] have concluded that neoplasms and tuberculosis are the commonest causes of hemorrhagic pleural effusions.

Although exudates, such as the effusions caused by inflammatory and neoplastic processes, tend to have higher specific gravity and concentration of protein than do transudates, chemical studies of serous exudates have not been found useful in making a diagnosis except in rare instances.[4,5,7,11,13,14,19,53]

Moore and Van Slyke[37] demonstrated that the specific gravity of the blood plasma parallels the concentration of protein in the plasma with sufficient exactness to indicate the con-

centration of the latter. The maximal deviation in their cases was 0.6 gm. per 100 cc. of plasma. A variation on their formula was found by Weech and his associates[56] to be accurate in working with transudates in dogs, and by Paddock[40] to apply in serous effusions from human beings. The formula is: grams of protein per 100 cc. of plasma $= 353.1\ (G - 1.00759) \pm 0.058$. G represents the specific gravity at 20° C.

Materials and methods: For this study 103 specimens of fluid from ninety-two consecutive patients with ascites, pleural effusion or pericardial effusion who underwent paracentesis, thoracentesis, pericardial aspiration, peritoneoscopy or laparotomy were collected and studied. The gross appearance of the fluid was noted and the specific gravity was determined with the ordinary laboratory hydrometer as soon as the fluid was obtained.

At first erythrocyte and leukocyte counts were attempted, but because so many of the specimens were grossly contaminated by blood in the operating room and because many of the cells had settled before time was available for the study, thus making results inaccurate, these determinations had to be abandoned before they were made on all fluids and are not reported. However, remarks as to the relative cellularity of the fluids, estimated from the appearance of the slides, were recorded throughout.

Specimens were centrifuged at 1,800 to 2,000 rpm for 15 minutes and the sediments obtained were smeared on slides and dried in the air at room temperature. Some of each set of slides were then fixed in 10% solution of formalin for 12 to 24 hours, stained with hematoxylin and eosin, and mounted with cover slips in Canada balsam. Other smears were stained by hematologists with Wright and Giemsa stains in their usual manner for preparing blood smears.

A differential count of lymphocytes, polymorphonuclear leukocytes and monocytes was made. The number of mesothelial cells, including malignant cells in this class when they were present, was noted for each 100 leukocytes.

Smears of each specimen were examined carefully for the presence of abnormal cells, often with the oil immersion lens when its use was needed to examine the nuclear detail closely.

Clinical pathologists assisted by determining the total concentration of protein, nonprotein nitrogen and chloride in the fluid.

In most instances cultures for bacteria were obtained. In many instances guinea pigs were inoculated with some of the fluid and subsequently necropsy was performed in the Section on Bacteriology.

Finally, the histories for all the patients were checked to discover the diagnoses and, as far as possible, to determine the subsequent course of the disease. As more than five years had elapsed since the beginning of the study, this was often of much interest.

Observations: Fifty-three specimens of fluid were obtained in 46 cases in which a diagnosis of malignant disease had been made clinically, on roentgenologic examination, biopsy or necropsy, but in only 34 cases in which 40 specimens were obtained, was there any evidence that the tumor might have involved the serous surfaces. In 19 (20 specimens) of the 34 cases a positive diagnosis of malignant disease could be made on the basis of the finding of malignant cells in the fluids. All fluids in which findings were doubtful were classified as negative for malignant disease.

Four specimens of fluid were obtained in the same number of cases in which a diagnosis of possible malignant diseases had been made. No positive results were found on examination of the smears.

Among the 46 specimens from 42 patients who did not have malignant disease, one was considered to contain malignant cells.

A summary of the characteristics found on examination of the smears may be found in Table 1. Consideration was given chiefly to the finer cytologic characteristics of the individual cells, such as the presence of mitotic figures, large, deep-staining nuclei and large, prominent nucleoli. Smears stained with Wright or Giemsa stain were often useful because of the greater demonstration of nuclear

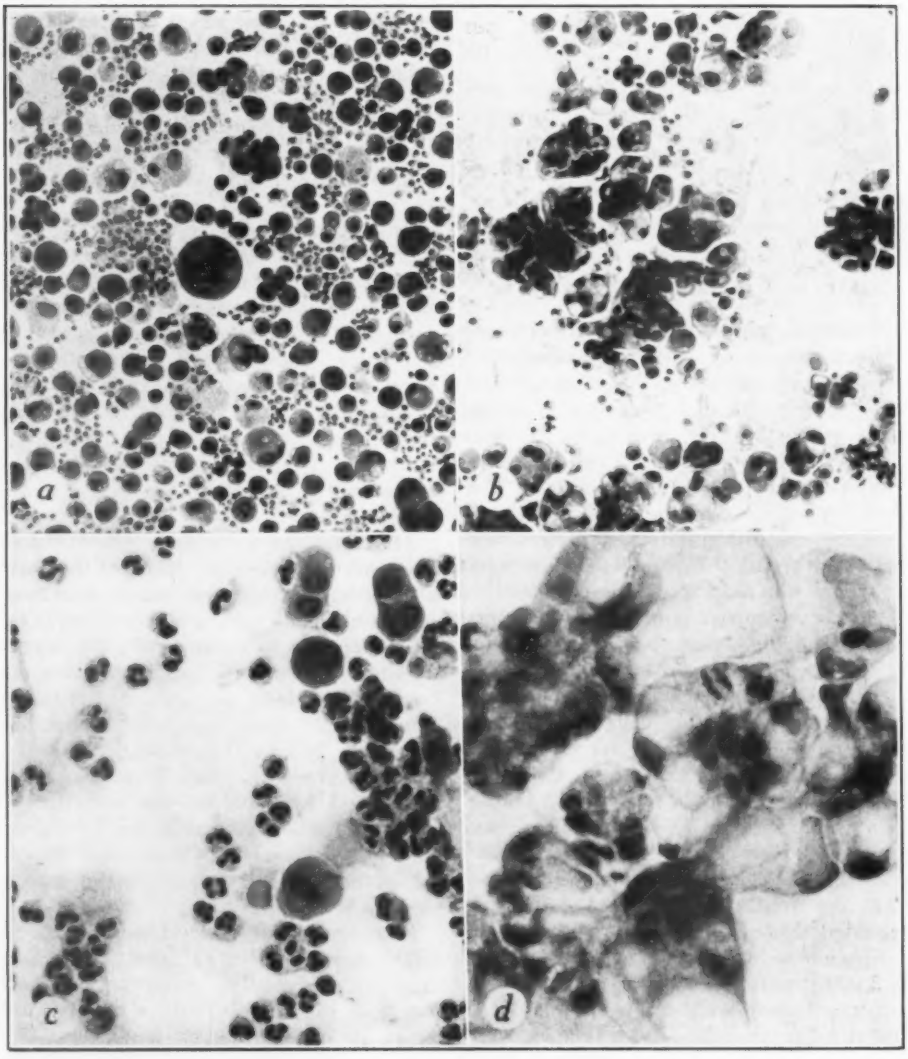

Fig. 1—Hematoxylin and eosin were used in each instance. **a.** Multinucleated giant cells and the generally large size of the malignant cells. Note the size of the leukocytes for comparison. Patient had carcinoma of the fundus of the uterus. Mitotic figures, large, prominent nucleoli and formation of acini were also seen in the smear. (x125.)

b. Formation of acini and signet-ring cells. Mitotic figures, multinucleated cells, large, prominent nucleoli, and acini are seen in other parts of the slide. Note the size of the lymphocytes for comparison. The peritoneum of the patient was studded with implants from a grade 4 (Broders' method) adenocarcinoma of the ovary. (x125.)

c. The metaphase of mitosis, multinucleation and a fairly large, prominent nucleolus. Note the size of the leukocytes for comparison. The smear also showed eccentric nuclei and irregular clumping of cells, but no organoid arrangement. The patient, 12 years old, had juvenile cirrhosis and was alive and well at least 4 years after this slide was made (x400).

d. Signet-ring cells in acini with a mitotic figure in anaphase. Note the size of the lymphocyte for comparison. The patient had implants of adenocarcinoma, grade 4, throughout the pelvic peritoneum as found on peritoneoscopy. (x400.)

detail than is afforded by hematoxylin and eosin. The presence of definite organoid arrangement of cells, such as in acini, was found to be a very useful diagnostic aid; no errors were made in this series when the presence of these cells was used as a criterion for the diagnosis of malignancy. The finding of eccentricity of the nucleus, formation of signet-ring cells, multinucleation and irregular clumping of the cells was not useful; they were found to occur frequently in fluid from patients without malignant disease. The erroneous diagnosis of malignancy was made on the basis of the finding of several mitotic figures in fluid which also showed eccentric nuclei, clumping and multinucleation. The patient was a boy with juvenile cirrhosis. He was alive and well at least 4 years later.

Fig. 1 shows some of the cellular characterictics mentioned.

Specific Gravity.—In fluid containing malignant cells the specific gravity ranged from 1.011 to 1.027, with an average of 1.022. In cases of malignant disease in which malignant cells were not found in the fluid the range was 1.012 to 1.030, the average being 1.020. In cases of nephritis the range was 1.006 to 1.012, with an average of 1.010. The range in cases of cirrhosis was 1.008 to 1.020; the average, 1.013. The specific gravity of the fluid in two cases of cardiac decompensation was 1.018 and 1.020. In the mis-

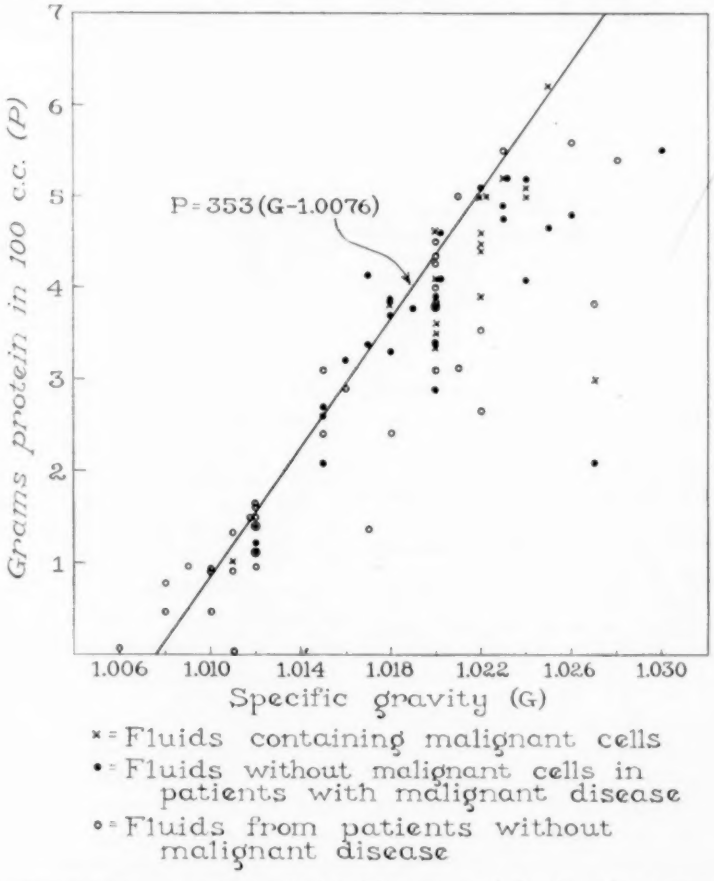

Fig. 2. Concentration of protein calculated by means of the formula of Weech and his colleagues.[66]

cellaneous group in which the conditions were chiefly inflammatory, the range was 1.015 to 1.028; the average, 1.020. The only tuberculous effusion in the series had a specific gravity of 1.026.

The formula of Weech and his associates was used to calculate the concentration of protein in the fluids from the specific gravity,[18,46] and the results are represented graphically in Fig. 2. It may be seen that the values deviate considerably from the straight line represented by their formula and that the scatter is greatest for the fluids with high concentration of protein and specific gravity. The amount of variation, however, has no relationship with the disease causing the formation of fluid. It may be seen further that there is so much spread of the values for protein in the fluids in cases of any type of disease that this factor is of no use in making a diagnosis in any individual case.

It was noted that fluid containing malignant cells tended to have a larger amount of sediment than others, but to a degree which could be considered as suggestive only in extreme cases. Except in purulent fluids, most of the fluid, regardless of the disease present, had a predominance of lymphocytes over polymorphonuclear leukocytes. Exceptions to this tendency occurred irregularly in all types of cases. A high number of mesothelial cells in relation to the number of leukocytes was ordinarily found when malignant cells were present, but sometimes a high number was found when malignant cells were not present.

Concentrations of nonprotein nitrogen and chloride in fluid varied over a considerable range without relation to the disease present. Correlations with those in the blood were unavailable for this study.

Comment. An attempt should be made to account for the presence of serous effusions in cases of malignant disease in which the diagnosis cannot be confirmed by examination of the fluid. Malignant cells will be found in the fluid only if the malignant process involves the serous surface. Under this circumstance cells and groups of cells may break off and float free in the fluid, and the surface may become seeded with daughter tumors if some of these cells are able to become implanted and grow.[5] If the number of free-floating cells is small they may not be found in the material examined because of their scarcity.

On the other hand, fluid may be formed in malignant disease in which the serous surface is not involved by the tumor. The inflammatory reaction about a carcinoma of the colon, for example, might be sufficient to cause ascites to form, even though the tumor cells had not penetrated the serosa. Malignant tumors of the ovary might well cause ascites through the same, poorly understood mechanism as do fibromas in Meigs's syndrome.[33,47] Metastasis to the liver through venous channels may cause venous obstruction in the liver and ascites through the same mechanism as cirrhosis. Ascites could be caused by blockage of the lymphatic channels in the regional lymph nodes by metastasis, but the ascitic fluid then should be chylous and it seldom is in actual practice.

Lymphatic obstruction could cause pleural effusion without serosal involvement, and the fluid would not necessarily be chylous unless the thoracic duct were impinged upon. Here again, the effusion might result from ovarian tumors, as in Meigs's syndrome.[33,47] Fluids may collect in cases of inflammatory conditions also without serosal involvement, especially if bronchial obstruction is present.

Summary. The diagnosis of malignant disease was made by study of the characteristics of individual cells as seen in stained smears of the sediment obtained by centrifuging serous effusions in 19 of our 46 cases of malignant disease in which the fluid was examined. Absence of the charac-

teristic cell did not rule out the diagnosis. The use of Wright and Giemsa stains for the smears in addition to hematoxylin and eosin was found to be of some assistance in some cases because they revealed the intranuclear detail more clearly. The value of bacteriologic studies on pleural and ascitic fluids was not questioned or investigated in this study.

In general the fluid which might be considered to be an exudate had higher specific gravity than the transudates, but the values overlapped considerably. Specific gravity correlated fairly closely with the concentration of the protein in the fluid in most cases, but the correlation was not as close as had been reported by others. Knowledge of the specific gravity of a serous fluid was probably of as much value diagnostically as that of the protein content.

A large cell pack suggested the presence of malignant disease with involvement of the serous surface, but a small cell pack was of no significance in diagnosis.

Knowledge of the nonprotein nitrogen and chloride was of no value in determining the cause of serous effusions.

Differential counts were too variable to be of diagnostic value.

Malignant disease can cause the formation of serous effusions without involvement of the serous surface by tumor cells.

TABLE 1

CELLULAR CHARACTERISTICS OF THE FLUID

	Malignant disease		Possible malignant disease	Nonmalignant disease
	Case	Specimens		
Cases	46		4	42
Specimens		53	4	46
Malignant cells in contact with serosa	34	40	0	0
Diagnosis of malignant disease made on basis of fluid examination	19	20	0	1
Mitotic figures	11	11	0	1
Large, prominent nucleoli	22	24	0	0
Eccentric nuclei	17	17	2	20
Signet-ring cells	25	27	1	8
Clumping of cells	12	12	2	14
Formed acini	10	11	0	0
Multinucleated cells	28	29	4	8

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THE USE OF RADIOACTIVE IODINE IN THE DIAGNOSIS OF THYROID DISEASE

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Radioactive iodine when administered by mouth or by vein is concentrated selectively by thyroid tissue.[1] The use of the Geiger-Muller tube after the administration of radioiodine for localization of functional thyroid tissue, indigenous or metastatic, has become a generally accepted procedure. When metastases are present at a distance from the neck, simple detection of the focus of radioactivity has been sufficient for the conclusion that functional thyroid cancer is present. When it is necessary to obtain information about the distribution of thyroid tissue in or near the gland itself, a more exact technique is required. The ordinary Geiger-Muller tube has a large acceptance angle. Marinelli[2] has introduced a collimated Geiger-Muller tube (enclosed in a lead tube) which responds to radiation only when the source is located within a relatively small angle in front of the tube. We have used this device in order to obtain a graphic representation of the distribution of thyroid tissue. When correlated with physical examination, this method permits greater accuracy in diagnosis. Sixty patients with a variety of affections of the thyroid were studied. In this report results with representative types of diseases are presented.

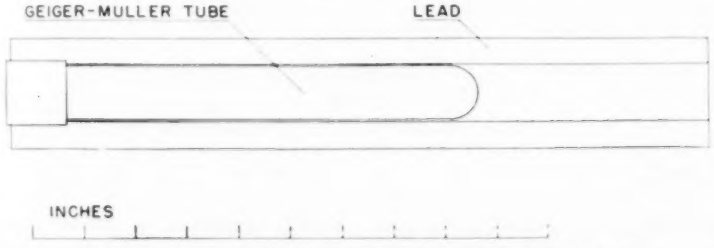

Fig. 1.—Diagram of the collimated Geiger-Muller tube.

Studies were made 1 to 2 days after the oral administration of I^{131}. Measurements were done with a Sylvania gamma counting Geiger-Muller tube enclosed in an open ended lead tube of 1" inner diameter made with a ½" wall thickness (Fig. 1). The whole assembly was supported on a portable X-ray tube stand. The "resolving power" of the collimating tube was

checked with two caps, ¾″ in diameter, containing the same amount of I^{131}. There was a distinct dip in the profile when the centers of the caps were 1″ apart.

The tube was first approximated to the skin at the level of the thyroid isthmus in the midline and the number of counts per second determined for a period of about 60 seconds (128 to 4096 counts). The tube was then moved laterally and measurements made at ½″ intervals without changing the level of the tube. Counts per second were plotted against distance from midline. We will refer to these graphs as "horizontal profiles."

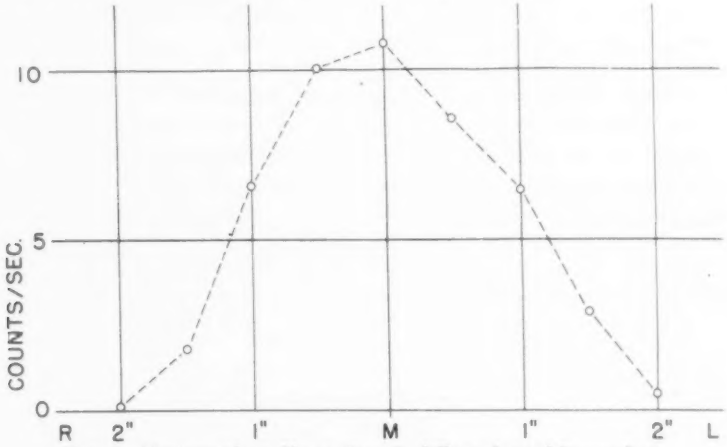

Fig. 2.—Horizontal profile in Case 1, diffuse thyroid hyperplasia.

"Vertical profiles" were obtained in a similar way. The tube was moved along the midline or parallel to it, and the counts per second were plotted against distance from the vertex of the skull (in inches). In taking the vertical profiles, the tube was approximated to the skin in each position. In addition to these studies, surveys of the limbs and pelvis for metastases were made routinely but were not plotted.

Typical curves in 7 representative cases are presented below, with brief clinical abstracts.

Case 1: J.F. Diffuse toxic goiter. This 53 year old Puerto Rican woman was admitted to the hospital with a 10 month history of swelling of the neck, dyspnea, palpitation, 60 pound weight loss, nervousness, and sweating. Physical examination revealed a thin nervous female with a diffusely and symmetrically enlarged thyroid estimated to weigh about 100 grams. The basal metabolic rate was plus 64%. After administration of 0.1 mc. of I^{131}, a horizontal profile was determined (Fig. 2).

The profile is symmetrical. This has been seen in hyperplastic thyroids and in normals. The apex of the triangle is occasionally flattened and broadened when the lateral lobes are greatly enlarged.

Case 2: I.M. Aberrant lingual thyroid. This 20 year old girl was admitted with a chief complaint of difficulty in swallowing. Eight years prior to admission similar dysphagia had caused her admission to another hospital where a growth at the base of the tongue was excised. Five years prior to admission, the symptoms, which had been relieved, began to recur and increased in severity until admission. There were no symptoms suggesting hyperthyroidism. Physical examination revealed a red, firm, nontender mass 1″ in diameter at the base of the tongue in the region of the foramen caecum. The thyroid was not palpable in the neck. The basal metabolic rate was plus 3%. X-ray

of the chest was normal. After administration of 0.5 mc. of I^{131} a vertical midline profile was determined (Fig. 3). The horizontal profile was symmetrical as in Case 1.

The apex of this profile is at the level of the tongue (9″ below the vertex), as compared to a normal profile, with the apex at the level of the cricoid (12″ below the vertex). This demonstrates the presence of functioning thyroid tissue at the level of the tongue. The absence of an increase of counts at the level of the neck shows the absence of a functional thyroid gland in the usual position. The preoperative diagnosis of aberrant lingual thyroid gland was made; in the absence of a normal thyroid, operation was not advised. Biopsy showed lingual mucosa with subjacent thyroid tissue, microscopically and on autoradiographs.

Case 3: D.T. Nontoxic thyroid adeno-

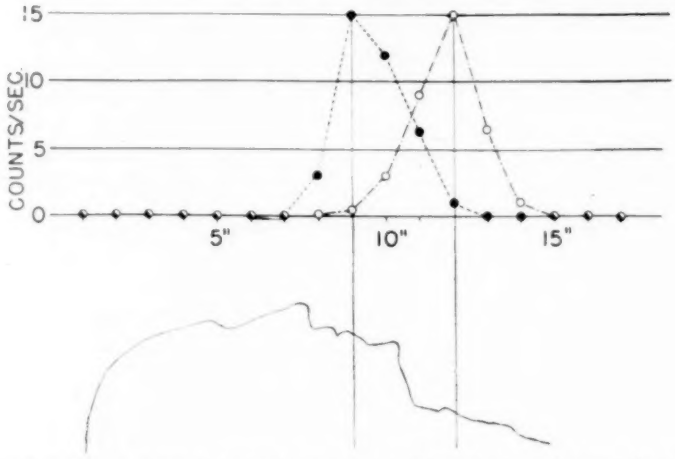

Fig. 3.—Vertical profile in Case 2, lingual thyroid. Solid circles are the record of the patient. The open circles are the profile of a normal patient.

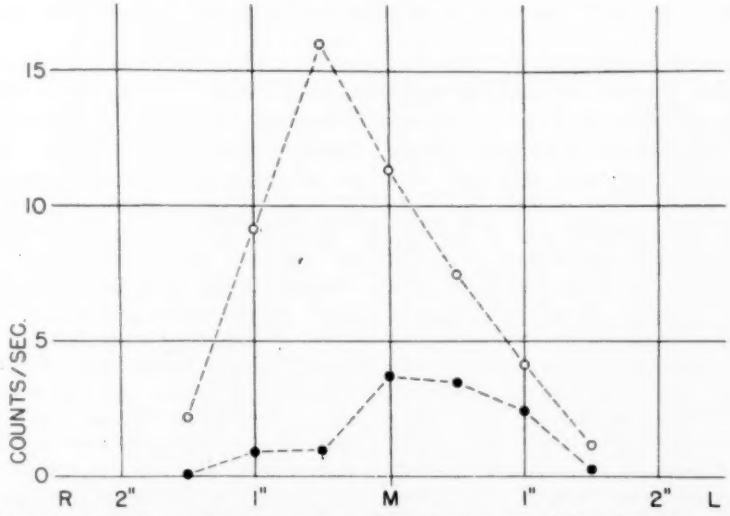

Fig. 4.—Horizontal profile in Case 3, nontoxic thyroid adenoma of the right lobe. The open circles are the preoperative profile; the closed, the postoperative.

ma. This 25 year old female was admitted with 4 month history of gradual swelling of the neck. There was no pain. There were no symptoms of thyroid toxicity. Physical examination showed no abnormality other than a palpable nodule, plum sized, in the right lobe of the thyroid gland. The basal metabolic rate was plus 1%. The patient received 0.5 mc. of I^{131} and a horizontal profile was determined (Fig. 4). The mass was resected by subtotal right hemithyroidectomy and the diagnosis confirmed.

The preoperative profile shows the maximum radiation ½" to the right of the midline. The area under the curve to the right of the midline is noticeably greater than that on the left; this corresponds to the physical findings. Postoperative profile showed the removal of most of the right lobe; almost all the uptake on that side had disappeared.

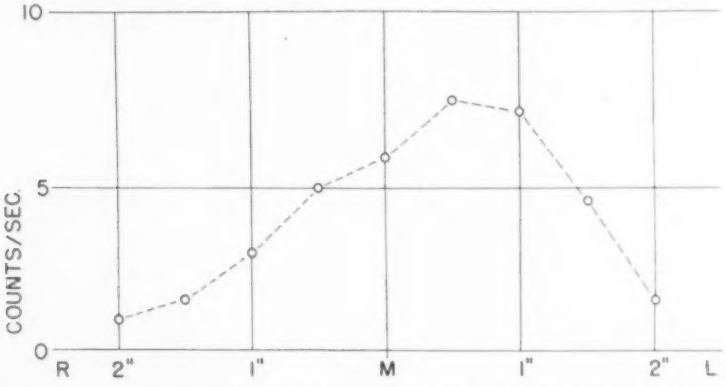

Fig. 5.—Horizontal profile in Case 4, colloid cyst of the right lobe of the thyroid.

Case 4: B.C. Colloid cyst of the thyroid. This 65 year old female presented herself with a two week history of pain in the right side of the neck. The pain had appeared suddenly on awakening and had maintained an aching character for most of the subsequent period. The patient observed a mass develop in the right side of the neck. There were no symptoms of hyperthyroidism or of hypothroidism. There was no recent weight loss or loss of appetite. In the right side of the neck there was a peach-sized mass which was soft above and firm below. This mass moved with swallowing and was not fixed to the skin or underlying tissue. The basal metabolic rate was plus 3%. After administration of 0.4 mc. of I^{131}, a horizontal profile was recorded (Fig. 5). The preoperative clinical diagnosis was thyroid adenoma or carcinoma; it was surmised that hemorrhage might be responsible for the sudden pain and swelling. At operation, hemorrhage into a colloid cyst was found. The lesion was removed. There was no evidence of malignancy.

The profile shows maximum radiation ½ to 1" to the left of the midline on the side opposite to the palpable mass. This suggests, in contrast to Case 3, that the mass was not composed of functioning thyroid tissue. Similar findings have been observed in other cases of colloid cyst and also in cases of anaplastic carcinoma.

Case 5: M.S. Aberrant thyroid. This 26 year old woman had noted gradual swelling of the right side of the neck for three months prior to admission. There were no metabolic disturbances. At another hospital tissue was obtained by aspiration and was reported as papillary carcinoma of the thyroid. Physical examination revealed a smooth, freely moveable thyroid gland of approximately normal size. In the right cervical region, under the sternomastoid muscle, there were two firm masses each about 1" in diameter.

No other nodes were palpable. The basal metabolic rate was minus 9%. 0.5 mc. of I^{131} was administered and a horizontal profile recorded (Fig. 6). Studies over the remainder of the body revealed no radioactive foci. A right radical neck dissection was performed with right hemithyroidectomy and subtotal left hemithyroidectomy. Three retrosternomastoid nodes replaced by aberrant papillary adenoma of the thyroid were reported. The thyroid tissue was not abnormal. Radioautograph of the nodes showed uptake of I^{131}.

The preoperative profile shows a marked maximum to the right of the midline. In view of the antecedent biopsy this was considered indicative of metabolically functional carcinoma. The postoperative profile is consistent with complete removal of functional tissue from the right side of the neck. Similar curves have been found in cases of functional unilateral carcinoma. It is planned to repeat the profile at intervals of 3 months to detect any recurrent growth of thyroid tissue on the left.

Case 6: E.C. Recurrent carcinoma of the thyroid. This 37 year old male was well until 1940 when a painless lump in the right side of the neck developed. This was biopsied; radiotherapy given for the next three years. The pathologic report is not available. In 1943 a right radical neck dissection was performed. Papillary carcinoma of the thyroid was found. Recurrent masses were resected in 1944 and in 1945. Typical diabetes mellitus developed in 1947. Within the

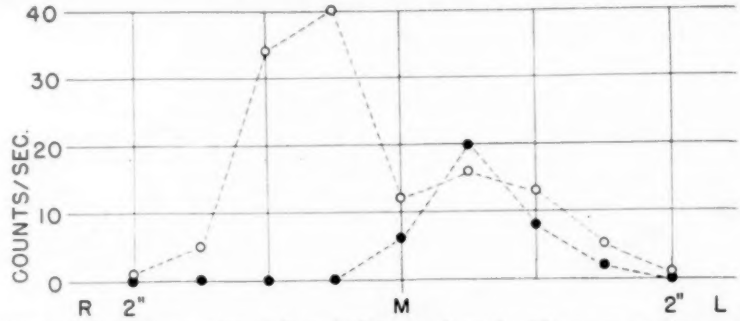

Fig. 6.—Horizontal profile in Case 5, lateral aberrant thyroid. The open circles are the preoperative profile; the closed, the postoperative.

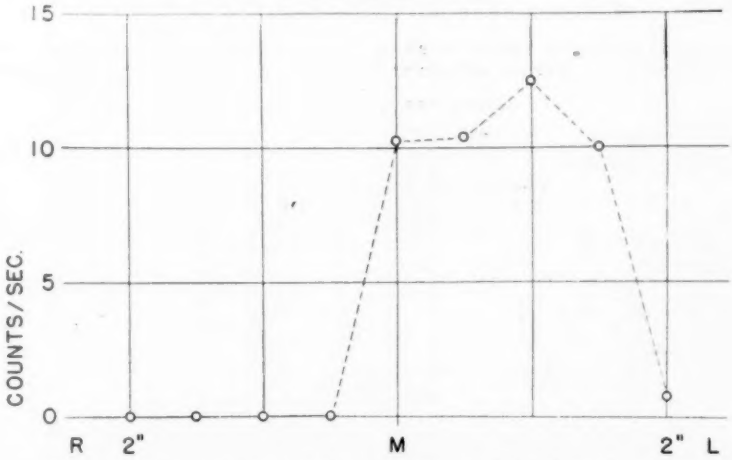

Fig. 7.—Horizontal profile in Case 6, papillary carcinoma of the thyroid with recurrence after right radical neck dissection.

few weeks prior to admission the patient noted the onset of dyspnea and productive cough. Considerable swelling developed at the right side of the neck. Physical examination revealed stony nodular masses 1″ to 2″ in diameter fixed to the deeper structures of the neck bilaterally. The right upper lobe of the lung presented signs of atelectasis. Roentgen examination confirmed this impression and bronchoscopy revealed metastatic thyroid tissue occluding the bronchus. The liver was palpable 3 fingers below the costal margin and was very nodular. After the administration of 3.0 mc. of I^{131}, profile studies were done (Fig. 7). The patient left the hospital against advice without further treatment or study.

The profile showed no measurable uptake of iodine on the operated right side; the curve is characteristic of unilateral radical dissection of the neck. This finding despite the palpable masses on this side led to the conclusion that the tumor was devoid of metabolic activity. Measurements over the chest and liver were at background level and supported this conclusion.

Case 7: A.F. Metastatic carcinoma of the thyroid. This 60 year old German born woman presented herself in May 1947 with known goiter of at least 30 years' duration. There were no toxic symptoms but local pressure had recently increased. The thyroid was nodular. The basal metabolic rate was plus 19%. Subtotal thyroidectomy was performed and primary adenocarcinoma was discovered in one of the goitrous nodules. Three months postoperatively, a mass, 1 inch in diameter, developed at the insertion of the right sternomastoid muscles behind the clavicle. Roentgen films of the chest revealed 3 large pulmonary infiltrations considered

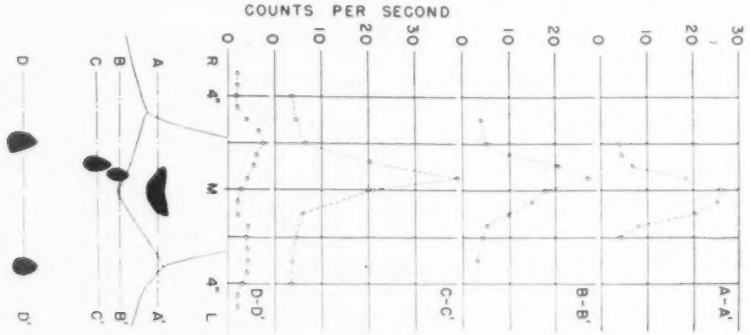

Fig. 8.—Horizontal profiles at various levels in Case 7, adenocarcinoma of the thyroid. The diagram represents the location of nodular metastases as demonstrated by Roentgen-ray.

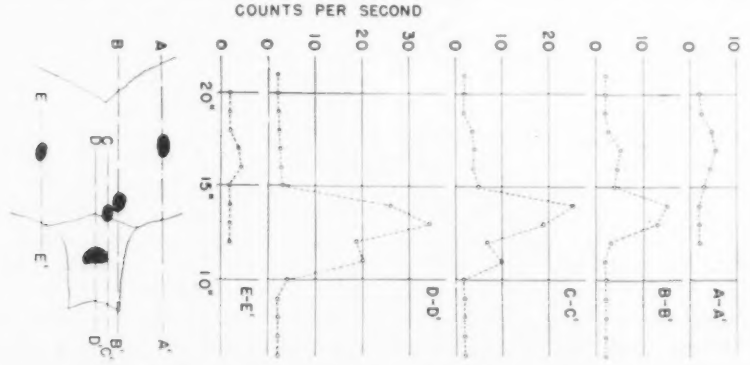

Fig. 9.—Vertical profiles in various planes, Case 7.

indicative of metastatic tumor. The patient remained asymptomatic. She was referred to this department where 3.0 mc of I^{131} was administered. Horizontal and vertical profiles were recorded (Figs. 8,9). Since the tumor exhibits distinct metabolic activity, for the metastases take up iodine, treatment has been instituted with repeated doses of 50 mc. of I^{131}.

In both sets of profiles the nodular masses in the chest are clearly demonstrated by local increases in radioactivity. From these a diagnosis of functioning thyroid metastases seems clear. Residual thyroid tissue in the neck is also demonstrated. The large tracer dose in this and the previous case was used in an attempt to insure uptake sufficient for detection of small metastatic masses situated deep in the chest.

Discussion. The cases discussed show that systematic measurements of iodine uptake and plotting of "profile" curves not only demonstrate the presence or absence of thyroid tissue, but also give information about its relative size and distribution. However, external measurements of radiation cannot be used definitively in the diagnosis of thyroid disease. Certainly in the neck, one cannot distinguish between colloid cyst and metabolically inactive carcinoma, nor between adenoma and active carcinoma. Furthermore, an inactive tumor surrounded by normal thyroid tissue may be confused with an active one. The method is therefore valid only for preliminary studies and should be supplemented by biopsy and radioautograph.

Summary: 1. A method for measuring and recording localized collections of administered radioisotopes is described.

2. The use of the method in representative cases of thyroid disease is shown and the limitations are discussed.

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ANTIGEN TRACER STUDIES AND HISTOLOGIC OBSERVATIONS IN ANAPHYLACTIC SHOCK IN THE GUINEA PIG *

Part I

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ONE of the most disputed aspects of anaphylactic shock is the location of the antigen-antibody reaction. Two main theories have developed regarding the reaction site. The cellular theory states that the antigen combines with antibodies fixed to cells, while the humoral theory maintains that the reaction occurs with antibodies in the circulating blood.

By using an antigen labeled with radioactive iodine and employing tracer techniques, we have been able to locate significant antigen concentrations during anaphylactic shock.

The finding of antigen localized in edematous bronchial fibrous tissue suggested our subsequent study to determine the relation of this localization to bronchial obstruction, which is such a striking feature in death of guinea pigs from anaphylactic shock. In this work we studied the stages in the development as well as the final picture of bronchial obstruction during shock and also the bronchial obstruction produced by various pharmacological agents acting on smooth muscle.

Materials and Methods. *Antigen preparation.* Partial iodination of bovine gamma globulin† with I^{131}, radioactive isotope of iodine§, gives a stable, radioactive, antigenic compound. An alteration in the antigenic specificity of a completely iodinated protein has been described by Wormall,[11] but we found no change in antigenicity resulting from only partial iodination.

A modification of the iodination technique described by Fine and Seligman[7] was used. In preparing the iodine solution, carrier iodine was used in addition to I^{131} to give color to the solutions and thereby facilitate extraction. To a sodium-iodide solution sufficient to give 1 mg. I^2 we added approximately 20 mc. of carrier-free I^{131}; then we added a few drops of hydrochloric acid and sodium nitrite to change the iodide to free iodine. The iodine was first extracted from this solution with carbon tetrachloride, then in turn extracted from the carbon tetrachloride by the following alkaline protein solution: 0.1 gm. of bovine gamma globulin dissolved in a mixture of 1.8 cc. water and 0.5 cc. 20% sodium carbonate. The iodinated protein solution was dialyzed against cold running tap water for 48 to 72 hours. Between 25% and 30% of

* This work was done under Contract from the Office of Naval Research.

† Bovine gamma globulin Fraction II has a mol. wt. of approximately 150,000. It is homogeneous in electrophoretic behavior. The material used in these experiments was generously supplied by Armour and Company, Chemical Research and Development Department, Chicago, Illinois.

§ The radioactive iodine used in this work was supplied by Oak Ridge National Laboratories, Oak Ridge, Tennessee.

the I^{131} used was incorporated in the protein molecules, an average of 3 iodine atoms per molecule of protein. About 5% of the iodine was lost in the two extractions and 65% to 70% failed to unite with the protein and was removed by dialysis. After 48 to 72 hours of dialysis, less than 1% of the remaining iodine could be found in the protein-free filtrate.

The iodine was tied to the tyrosine molecules in the two ortho positions relative to the hydroxyl group.[11] The stability of this chemical linkage was tested by Fine and Seligman,[7] who found that trypsin hydrolysis at 37°C and pH 8 for 6 hours released only 4% of the I^{131} from the protein. We found that after 24 hours at room temperature in aqueous solution at pH 10.5 only 0.5% of the I^{131} was split from the protein and at pH 5 only 1.3%. Twenty-four hours in any of the organic substances used in tissue preparation of autoradiograms (absolute alcohol, dioxane, ether, and paraffin) removed less than 3% of the I^{131} from the protein. Thus, it seemed to us safe to assume that the I^{131} protein linkage was stable under the experimental conditions.

Experimental Procedures. Twenty-six male guinea pigs weighing from 300 to 350 gm. were used in preliminary antigen assays and antigen tracer experiments. Ten were used to determine the range of minimal lethal anaphylactic shock doses using non-radioactive iodinated protein prepared as described above without the addition of I^{131}.

Nine were given sensitizing injections intraperitoneally consisting of 60 mg. of non-radioactive iodinated protein. After a period varying from 2 to 5 weeks, minimum lethal shock doses (from 2.5 mg. to 10 mg.) of radioactive iodinated protein were injected into the left femoral veins. Shock was fatal within 5 to 8 minutes to all but 2 pigs, which were killed by a blow to the head 8 minutes after injection.

Seven non-sensitized control pigs were given intravenous injections of radioactive antigen (from 2.5 to 15 mg.) and killed by a blow to the head 8 minutes later.

In order to study the mechanism of bronchial obstruction, we used 21 additional guinea pigs. Ten were given sensitizing and shock injections as in the antigen tracer experiment above but were killed in various stages of shock from 1 to 4 minutes after the injection of the shock dose. Six were injected intravenously with fatal doses from 0.2 to 0.5 mg. of histamine. Five were given fatal intravenous injections of 0.1 mg. of Doryl.

Our control animals were killed by either a blow to the head or by intraperitoneal injection of nembutal. The cause of death did not affect the appearance of the lungs.

Histologic study of all the animals was carried out with special emphasis on the site of antigen concentration and mechanism of bronchial obstruction.

Two techniques were employed to locate the antigen within these guinea pigs. First, the amount of radioactivity per gram of blood, lung, liver, spleen, lymph node, striated muscle, kidney, thyroid, brain, and testis was determined by use of a Geiger counter. Error due to self-absorption was eliminated by filtration equivalent to 1.75 mm. of aluminum calculated to stop all beta radiation from I^{131} and allow only the gamma rays to be counted. Second, the histologic location of the antigen was determined by autoradiograms made from the only two organs containing significant amounts of radioactivity: the lung and liver. Autoradiograms were made according to Evans'[6] method, by slicing tissues at 0.2 cm., fixing in alcohol formalin, and blocking in paraffin in the routine manner. Sections were mounted on lantern slide photographic plates, and allowed to expose in absolute darkness. Exposures varied according to the amount of radioactivity in the tissue and were calculated from Geiger counts of the sections. With filtration equivalent to 0.3 mm. of aluminum, sections registering .05 to .1 μc. gave satisfactory exposures in 2 to 3 weeks. After exposure the paraffin was removed from the sections with xylol and the plates were developed according to the usual method. Finally the sections were stained with Harris hematoxylin and mounted.

In an autoradiogram, radioactivity is evidenced by black granular silver deposits (Figs. 1 and 2). The sections show fair histologic detail, although the gelatin

emulsion of the lantern slide stains lightly, giving a blue background to the preparation which makes photography difficult.

Observations. Using sensitizing intraperitoneal injections of 60 mg. of non-radioactive iodinated protein and a 2-week sensitization period, we found the range of minimum lethal intravenous anaphylactic shock doses to be between 2.5 mg. and 5 mg. iodinated protein. Extension of the sensitization period to 6 weeks did not change this minimum range significantly.

The shock produced by this antigen was of the classic type. It began with sneezing and coughing, then development of a "lion's mane," respiratory difficulty, motor activity, convulsions,

Fig. 1.—Autoradiogram of a bronchus from a guinea pig dying in anaphylactic shock. The location of radioactive antigen is indicated by black granular silver deposit. The large blood vessel at left is filled with antigen. Antigen is also seen concentrated in the fibrous tissue around the bronchus. The smooth muscle immediately beneath the mucosa is conspicuously lacking in activity. This preparation was exposed for 1 week. (× 50)

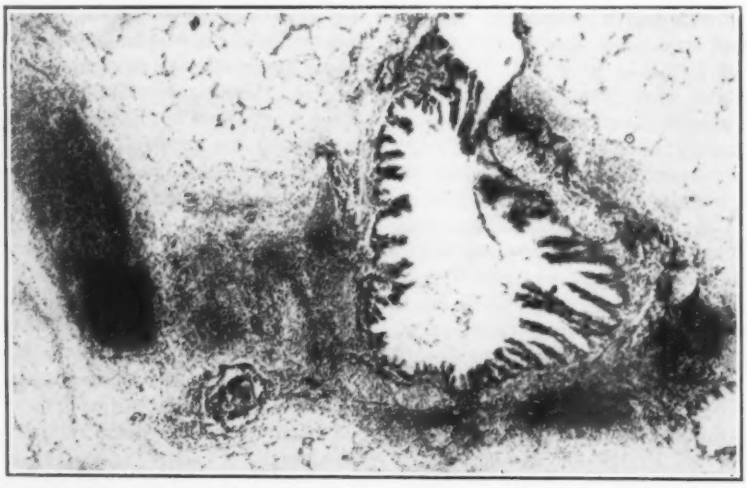

Fig. 2.—Autoradiogram made from same block as seen in Fig. 1. Exposure time of 3 weeks was used to accentuate antigen concentrations. (× 50)

incontinence, and death within 5 to 8 minutes.

The autopsy radioactivity determinations of all the organs and tissues showed the greatest antigen concentration to be in the blood. Approximately 70% of the fatal shock dose of antigen injected into the sensitized animal was in the blood at time of death, about 85% of the antigen injected into non-sensitized animals was in the blood 8 minutes after the injection. This means, of course, that all tissues would show some radioactivity because of the contained blood. Of all the tissues examined, only lung and liver showed significant concentrations of radioactivity.

A significant part of the radioactivity in the liver and a smaller part of that in the lungs was due to the presence of blood containing activity. However, since these organs contained a much greater activity concentration than other vascular organs, such as spleen and kidney, they also had a specific uptake of antigen. The tissues other than lung and liver had only traces or, rarely, small measurable amounts of activity, up to 30% of the amount found in the liver. These small amounts of activity could be explained on the basis of contained blood.

The activity concentrations for blood, lung, and liver are given in Table 1. For each animal the activity in 1 gm. of blood has arbitrarily been set at 100, in order to establish a base line for comparison, and the values for lungs and liver calculated accordingly. The activity concentration in the lungs of animals dying in shock was about twice that in the lungs of the controls. The livers of both groups, however, contained nearly equal concentrations of activity. The 2 sensitized pigs which in spite of apparently adequate shock doses did not have fatal shock, had only two-thirds the lung activity concentration found in the controls and about one-third that found in their fatally shocked mates. The livers of these animals showed a slightly higher activity concentration than those of other animals.

Autoradiograms of lungs and livers of these non-sensitized controls and of the sensitized guinea pigs revealed several important findings.

The lungs of the non-sensitized animals showed considerable activity with-

TABLE 1. ACTIVITY DETERMINATIONS ON BLOOD, LUNG, AND LIVER BASED ON ACTIVITY PER GRAM OF TISSUE

For each animal the activity of the blood is set at 100 and the activities of lung and liver are calculated accordingly.

Non-Sensitized Control Guinea Pigs

Animal	Protein Injected (mg.)	Blood	Lung	Liver
120	3.4	100	43	40
121	3.4	100	31	50
128	2.5	100	31	36
129	5.	100	37	44
130	2.5	100	31	40
137	15	100	28	39
138	10	100	33	48
Average		100	33	42

Sensitized Guinea Pigs with Fatal Shock

Animal	Protein Injected (mg.)	Blood	Lung	Liver
110	7.5	100	57	38
113	10	100	87	64
114	2.8	100	69	34
115	5	100	55	24
122	2.8	100	56	37
123	2.5	100	56	36
124	5	100	63	37
Average		100	63	39

Sensitized Guinea Pigs with Non-Fatal Shock

Animal	Protein Injected (mg.)	Blood	Lung	Liver
111	5	100	22	43
117	2.5	100	22	55
Average		100	22	49

in the blood vessels but no appreciable amount in the tissue. However, the lungs of the sensitized pigs dying in shock showed, in addition to the activity within the blood vessels, a marked concentration of activity in the fibrous tissue surrounding the bronchi and their accompanying pulmonary arteries (Figs. 1 and 2).

The heaviest concentrations of radioactivity were in the edematous, congested, fibrous tissue between the bronchus and its accompanying artery and between the cartilaginous plates and smooth muscle sphincter of the bronchus. The smooth muscle about the bronchi and about the vessels contained no activity. The submucosal tissues and the mucosa of the bronchi contained very little radioactivity. This concentration of radioactivity had a somewhat irregular distribution, varying in amount both in bronchi of the same size and in different levels of the same bronchus. Almost all of the activity was found around bronchi large enough to have cartilage in their walls and the size of these bronchi appeared to have little to do with the amount of antigen concentration. The smaller bronchioles without cartilage and with little surrounding fibrous tissue only rarely had concentration of radioactivity in their walls. There was no significant amount of activity in the alveolar walls or interlobular septa.

In the lungs of the 2 sensitized pigs which did not develop fatal shock there was no significant concentration of activity about the bronchi or elsewhere.

The autoradiograms of the livers of both sensitized and non-sensitized animals were essentially the same. There was definite concentration of the radioactivity within the large blood vessels, but elsewhere there was more or less homogeneous scattering of less intense activity without any concentration in any particular part of the lobule or of the portal areas. There was a slight suggestion of concentration of the activity about the Kupffer cells, but accurate localization to such small structures was beyond the limitations of the technique.

The histologic study of these animals was directed primarily to the organs of antigen concentration: the lung and liver. The livers of control and shocked animals were indistinguishable. The lungs of these 2 groups, however, differed in several ways. After opening the thorax, the control lungs collapsed immediately to about ¼ the volume of the thoracic cavity while the shocked lungs remained fully distended as a result of the bronchial obstruction. On microscopic examination of the lungs of the fatally shocked guinea pigs, the alveoli and the air passages extending proximally as far as the small bronchi with associated cartilage plates, were widely distended with air. These same structures in normal, control lungs showed various degrees of collapse with consequent thickening of alveolar walls. The lumen of the bronchial tree proximal to the termination of the cartilage plates was approximately the same in both shocked and control pigs and therefore could not be accepted as a measure of the patency of the bronchial tree during life (Figs. 3 and 4). The smooth muscle of both appeared similar and the mucosa was thrown into tall folds which filled the lumen.

There was an important difference, however, between the peribronchial tissues of the shocked and control lungs. The fibrous tissue which surrounded the bronchi and their associated vessels and cartilage plates was normally a thin compact layer of collagenous fibers in which were found irregularly distributed small aggregates of lymphocytes and a network of inconspicuous capillaries and lymphatics (Fig. 3). In the shocked lungs, however, this tissue was distended to 3 to 5 times normal width

by intense edema in which were found enormously congested capillaries and lymphatics and a few scattered lymphocytes (Fig. 4). The edema and congestion were present around all bronchi with cartilage and occasionally around the smaller divisions but were not entirely uniform throughout. The ratio of amount of edema fluid to bronchial diameter was greatest in the secondary or medium-sized bronchi.

In the series of guinea pigs killed

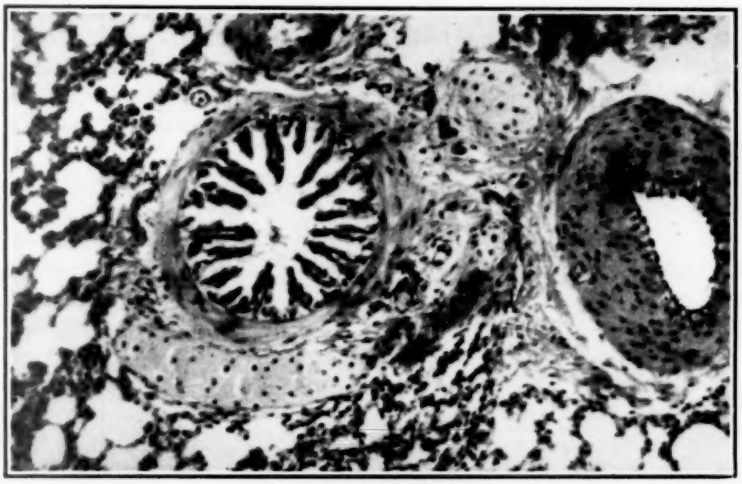

Fig. 3.—Medium-sized bronchus from normal control animal. The lumen is compromised by infoldings of mucous membrane. The fibrous tissue and vessels around the bronchus are inconspicuous. The cartilage plates are in close proximity to the smooth muscle coat. (× 115)

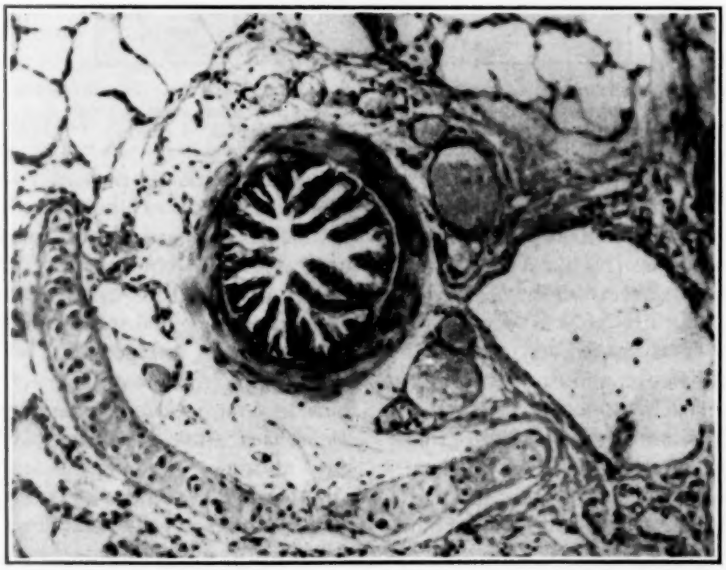

Fig. 4.—Medium-sized bronchus from animal dying in anaphylactic shock. Note close resemblance of lumen, mucous membrane, and smooth muscle to the structures seen in control, Fig. 3. The fibrous tissue is edematous and the blood vessels and lymphatics are congested. The cartilage plate is separated from smooth muscle coat by wide zone of edema. (× 115)

at various stages in the development of anaphylactic shock, we traced the pulmonary changes from before the onset of dyspnea to the final stage described above. Dyspnea appeared 1¾ to 2 minutes after injection of the shock dose. Up to this time and at the onset of dyspnea the lungs collapsed on opening the thorax as do normal lungs, but ½ to ¾ of a minute afterwards the lungs would no longer collapse on opening the thorax, although maximal distention was not seen until after 1½ to 2 minutes of dyspnea. Lungs were examined microscopically at the following intervals: (1) 1 to 1½ min. after shocking dose before onset of dyspnea; (2) 1¾ to 2 min. after shocking dose at onset of dyspnea; (3) 2½ to 2¾ min. after shocking dose ½ to ¾ min. after onset of dyspnea, and (4) 3½ to 4 min. after shocking dose 1½ to 2 min. after onset of dyspnea.

The bronchial congestion and edema previously described had already started to form around some of the bronchi before respiratory difficulty was evident. With the onset of dyspnea, the bronchial edema was not more marked but was seen around more of the bronchi. One half to ¾ of a minute following onset of shock there was a definite increase in the amount of edema and congestion, which progressed, and 2 minutes after onset of dyspnea there was ½ to ⅔ the amount of edema seen in the pigs dying of shock.

An interesting, but less easily evaluated, change was apparent in the smooth muscle of the bronchi. Just before the onset of dyspnea, there were irregular thickenings and contraction bands in a few of the smooth muscle sphincters apparently representing a mild degree of contraction. The number of bronchi thus involved increased and was at a maximum ¾ of a minute after dyspnea appeared. The number of bronchi with evidence of smooth muscle contraction was somewhat less 2 minutes after the onset of dyspnea, and at time of death some 2 to 4 minutes later there was no evidence of smooth muscle contraction.

Both of these changes described above would presumably cause a progressive rigidity of the bronchus which would interfere with its function.

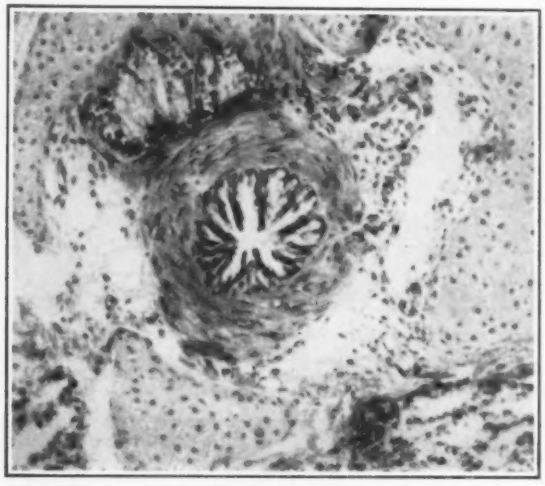

Fig. 5.—Medium-sized bronchus of animal dying 5 minutes after administration of Doryl with marked bronchial obstruction. The lumen of the bronchus is very small and the smooth muscle coat is thick and appears contracted. There is little or no edema. (× 115)

Effects of Pharmaceutical Bronchial Constrictors. Intravenous histamine injections produced shock similar to but more rapid than anaphylactic shock. The lungs from these animals dying 2 to 4 minutes after histamine injection were morphologically similar to those from cases of fatal anaphylactic shock.

Of the various parasympathomimetic drugs used, pilocarpine, physostigmine, and Doryl, only Doryl produced sufficient bronchial obstruction to keep the lungs distended after the thorax was opened. The degree of bronchial obstruction in these lungs was greater than that seen in anaphylactic shock and was caused solely by a marked contraction and thickening of the bronchial smooth muscle coat (Fig. 5). There was no bronchial edema or congestion. The degree of smooth muscle contraction in these lungs was much greater than that seen in the shocked pigs as indicated by markedly increased thickening of the smooth muscle coat and more definite contraction bands.

Comment. In anaphylactic shock caused by intravenous injection of minimal lethal shock doses of iodinated bovine gamma globulin, about 70% of the antigen is found in the blood at time of death. This represents an escape of twice as much antigen from the circulation as occurs in non-sensitized animals in the same time interval.

There was a specific increase in antigen uptake in the lungs after sensitization. Sensitized lungs took up twice as much antigen as control lungs in an equal time. The other organs and tissues did not show any change in affinity for antigen after sensitization. The antigen was found in the loose, edematous bronchial collagenous connective tissue. A part of the antigen found in this edematous region could be explained on a non-specific basis, due to protein containing fluid leaking from the blood vessels. However, control studies with non-specific labeled proteins in the blood stream during anaphylactic shock indicated that such protein leakage in the edema formation does not account for the entire antigen concentration around the bronchi.

The antigen concentration and distribution and the histologic appearance of the liver were the same in sensitized and control animals. This suggests a non-specific phagocytic reaction on the part of the liver since it was unchanged by sensitization or shock.

We did not find satisfactory histologic evidence to support the usual assumption that bronchial obstruction in anaphylactic shock is due solely to smooth muscle contraction. This assumption has been based largely on 2 observations: first, the histologic observation of bronchial stenosis in fatally shocked guinea pigs, which was interpreted as due to smooth muscle contraction. In 1910 Auer and Lewis[2] as well as Anderson and Schultz[1] found fatal asphyxia in anaphylactic shock in guinea pigs, which they thought to be due to bronchial obstruction resulting from contraction of bronchial smooth muscle. Schultz and Jordan,[10] and Biedl and Kraus,[3] noted no great difference between the bronchial lumens and smooth muscle of control and shocked lungs. But in spite of this observation they, too, assumed the bronchial obstruction in anaphylactic shock was due to smooth muscle contraction. Although bronchial edema was noted by some of these workers,[10] it was not considered to contribute to the bronchial obstruction.

Second, the fact that bronchial obstruction resulted from perfusion of partially and completely isolated sensitized lungs with the specfic antigen,[4] was interpreted in the light of the

Schultz-Dale phenomenon as being due solely to smooth muscle contraction. Such an interpretation is not, however, conclusive.

Since the fatally shocked lungs had obvious bronchial obstruction, evidenced by their failure to collapse after opening the thorax, one would expect their bronchi to be more constricted than those of normal lungs. Such, however, was not the case, and bronchi in both fatally shocked and control lungs had approximately the same internal diameters, and appeared to be equally compromised by large infoldings of mucous membrane. It is clear therefore that the size of the bronchial lumen seen in microscopic sections cannot be accepted as a measure of the patency of the bronchial tree during life. The smooth muscle in both types of lungs also appeared the same with no convincing evidence of contraction in the shocked lungs. There was, however, a significant difference in the bronchial fibrous tissue, which in the controls was compact and inconspicuous but in the shocked animals was distended with edema to 3 to 5 times its normal thickness. It seemed probable that the extreme rigidity and associated compression of the bronchi caused by the edema could account for most of the bronchial obstruction evident in the shocked lungs.

Study of the stages in the development of anaphylactic shock showed evidence of smooth muscle contraction, thickening of the muscle and contraction bands, only in the early stages, just preceding and for 2 minutes immediately following the onset of dyspnea. At the time of death, 5 to 8 minutes after antigen injection, there was no evidence of smooth muscle contraction. In more rapidly fatal anaphylactic shock produced by egg albumin where death occurs in 2 to 3 minutes, bronchial edema similar to that described here is present, but there is also evidence of smooth muscle contraction about the bronchi at time of death. These observations are supported by Manwaring's work on anaphylactic shock in the dog.[9] He found that the smooth muscle of the uterus, bladder, and intestine began to contract 45 to 75 seconds after the shock injection. The contraction reached a maximum in 2 minutes, and then began to subside. Thus it would seem that smooth muscle contraction in anaphylactic shock might be transitory, occurring in the first few minutes of shock. If shock is fatal within this period, bronchial smooth muscle contraction as well as edema is evident. If, however, the shock is more prolonged, as in our experiment, the degree of contraction of the smooth muscle diminishes and at time of death there may be no evidence of smooth muscle contraction. In such cases the bronchial edema is the only apparent explanation of the bronchial obstruction.

Bronchial edema in the guinea pigs began to form shortly before the onset of respiratory difficulty and increased progressively, being extensive enough 2 minutes later to account for a large part of the bronchial obstruction. At the time of death, this edema was sufficient to account for most, if not all, of the bronchial obstruction.

Bronchial edema was noted by earlier workers[10] and thought to be due to smooth muscle contraction. However, since no edema resulted from the marked bronchial smooth muscle contraction following the administration of Doryl, this conclusion does not appear entirely correct. In studying the anaphylactic reactions of isolated organs in the guinea pig and dog, Manwaring[8] found much perivascular edema, and suggested that the resulting local tissue pressure might be a factor in increased perfusion resistance occurring in shock. He did not, however, suggest that this increased tissue pressure was a partici-

pating factor in bronchial obstruction.

The concentration of antigen in the edematous regions suggests a causal relationship between the presence of antigen, or of the antigen-antibody reaction, and a change in vascular dynamics resulting in the formation of edema.

Because of the antibody storing role of the lymphocytes found by Dougherty, Chase and White,[5] we paid special attention to the lymphoid tissue, especially that of the lung. However, there was no evidence in our material that the lymphoid tissue takes any part in the localization of antigen.

The findings in the 2 non-fatally shocked guinea pigs suggests a decreased affinity on the part of the lungs for the antigen. The possibility of a hyposensitivity, or immunity, in these 2 animals would warrant further investigation.

The exact relation between antigen concentration and edema formation at this time cannot be determined. Investigations are under way now to study interim stages of the edema formation and antigen uptake in the bronchial walls during anaphylactic shock and the effects of various shock preventing drugs on antigen localization and edema formation.

Summary. 1. Significant amounts of labeled antigen were picked up only by liver and lung during anaphylactic shock.

2. The amount of antigen taken up by and its histologic distribution in the liver was the same in sensitized and non-sensitized animals and therefore presumably not related to degree of sensitivity.

3. The affinity for antigen on the part of sensitized lungs in fatal shock was about twice that seen in controls and therefore presumably a function of the sensitivity.

4. The increased amount of antigen taken up by the sensitized lungs was found in the edematous bronchial fibrous tissue.

5. We were unable to confirm the generally accepted assumption that bronchial obstruction of anaphylactic shock results solely from contraction of bronchial smooth muscle. Only in the early stages of shock (within 2 minutes after the onset of respiratory distress) was there convincing morphologic evidence of smooth muscle contraction; and even in these early stages there was already some edema formation. In the terminal stages of shock, the smooth muscle did not appear contracted or otherwise abnormal.

6. The bronchial edema which began to form during the early stages of shock became massive in the terminal stages and at that time appeared to be the most important factor in the production of bronchial obstruction. Since this edematous zone was the site of antigen localization, it seemed possible that the antigen-antibody reaction was related to the edema formation.

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THE MORPHOLOGICAL BACKGROUNDS OF "GENUINE LIPOID NEPHROSIS"

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In a previous communication[10] I tried to show that the introduction of the concept of "nephrosis" by Müller was an unfortunate one, since at present, students of renal disease are far apart in their interpretation of what is meant by this term. This is manifest in the widely diverse classifications of the "nephroses."

One reason for this conclusion is due to the fact that the original metaphysical concept of Müller has been modified. Beginning as a degenerative and non-inflammatory parenchymatous lesion, nephrosis has at various times been regarded as a series of widely unrelated morphological entities, and at other times a complex of clinical expressions without a precise morphological background.

After numerous vicissitudes the concept suggested by Epstein[4] was widely adopted, namely, that "nephrosis" was a malady characterized by albuminuria, hypoproteinemia, hypercholesterinemia, double refractile lipoid droplets in the urine, secondary anemia, edema or anasarca with a low protein content in the exudate, normal renal function and a normal blood pressure, a lowered basal metabolic rate and an exceptional tolerance for thyroid preparations. The morphological background was a "lipoid nephrosis." This is still termed the true or genuine nephrosis. This concept was a direct challenge to pathologists and it did not take long to discover that such a clinical and morphological correlation obtained in only the rarest of instances, and that in cases where the clinical expression was classic, a "lipoid nephrosis" was not found at post mortem, but usually a glomerulonephritis, less frequently an amyloid kidney, and rarely, the sclerotic kidney associated with hypertension. Nevertheless, despite the presence of glomerulonephritis and amyloid deposits in these kidneys, the organ showed one of the morphological features of a "lipoid nephrosis," namely lipoid deposition in the tubules and double refractive bodies in the urine. To reconcile these clinical and anatomical differences, the suffix "nephrotic syndrome" was added. In these cases it was correctly concluded that the lipemia was responsible for the lipoid deposition within the renal parenchyma, and that it was not a primary but a secondary event. Furthermore, it was soon discovered that many of the characteristic clinical features of a "lipoid nephrosis" occurred in extra-renal conditions, such as protein starvation, war edema, hepatic cirrhosis, in slow prolonged bleedings from whatever cause, in pernicious anema, in prolonged ulcerative intestional lesions and in sprue; and even in these, the kidney at post-mortem showed a greater or lesser degree of lipoid deposition. The common denominator in all these conditions was a hypoproteinemia, the result either of loss (albuminuria), deficient intake (hunger edema), failure of formation (liver cirrhosis), and probably, deficient absorption (sprue). That an anatomically perfect "lipoid

nephrosis" may be the result of an extrarenal factor is illustrated in the following case:

Case 1. J. H. (adm. 379773) male, aged 43, was admitted to the first medical service (Dr. George Baehr) on Jan. 28, 1933. Following pneumonia, he developed a persistent edema, first of the right leg, then of the left and finally of the abdominal wall. It was thought that the lower part of the inferior vena cava was involved by a thrombophlebitis which had extended upward from the femoral veins. Later the phlebitic process extended to the right jugular vein and to the axillary veins. He returned a year and a half later because of the persistent edema. The urine then showed 3 plus protein and granular casts. The blood pressure was 120 systolic and 75 diastolic. The blood urea was 19 mgm. per 100 cc. The total blood protein 5.2 gms. %, the blood cholesterol 734 mgm. per 100 c.c., the basal metabolic rate was minus 21%. It was thought that the patient had a subacute glomerulonephritis in the nephrotic phase. In spite of diuretics the edema did not improve. He was again discharged but returned three months later. The edema was very marked. The physical findings were similar to those found on the previous admission. He developed erysipelas and died.

Necropsy (no. 9587). Lipoid nephrosis, old thrombosis with recanalization of the inferior vena cava, renal, left adrenal, spermatic, common iliac, femoral and superior mesenteric veins.

Microscopic findings: The kidney parenchyma showed extensive deposition of fat. The epithelium of the tubules was flattened and there were occasional areas

Fig. 1.—Kidney from Case 1, appearing clinically as a "lipoid nephrosis" and found to be secondary to a thrombophlebitis of the renal veins.

of round cell infiltration in the cortex; with the exception of an occasional fibrotic glomerulus, the glomeruli were intact. There was slight increase in the interstitial connective tissue and some congestion between the tubules (Fig. 1).*

Epstein's admirable contribution was the application of Starling's[16] law to the explanation of most of the clinical phenomena of "lipoid nephrosis." His contention that the hypoproteinemia was the basic factor in the production of edema and anasarca has received full clinical and experimental confirmation[6,7,8]. This law also explains many of the edemas of extrarenal origin. The mechanisms whereby a hypoproteinemia may cause edema have been summarized in a previous paper[11].

That the lipemia bears some relation to the hypoproteinemia is acknowledged, the proof being that it has been experimentally produced by plasmophoresis, by bleeding and by experimental protein starvation. The kidneys under such circumstances also revealing lipoid deposition. The precise mechanism is not clear. There is a curious relation between the lipemia and the lowered basal metabolic rate so uniformly found in hypoproteinemic states. I submitted evidence[12] that the lowered metabolism in "nephrotic states" could be explained by the edema which, acting as a suit of clothes, prevented the dissipation of heat from the body. In fact, it was shown that any integumentary thickening was often accompanied by a low basal metabolic rate; for instance, icthyosis, the edematous stage of scleroderma, certain cases of congestive failure without dyspnea or tachycardia and true myxedema. In these conditions, a lipemia as represented by a hypercholesterinemia was almost invariably present. The lipemia accompanying lowered metabolic rates possesses all the ear marks of a compensatory phenomenon, but the precise mechanism is unknown. The genesis of lipemia in "lipoid nephrosis" may be represented by this sequence of events: hypoproteinemia → edema → lowered basal metabolism → lipemia (hypercholesterinemia).

The purpose of this discussion is to show that the lipoid deposition in the renal parenchyma is secondary to the hyperlipemia and that therefore a "lipoid nephrosis," in the anatomical sense, is not primary and therefore cannot be the background for the clinical manifestations, but rather, that it is the result of physico-chemical mechanisms sequential to a hypoproteinemia.

Divorced of a consistent morphological background, "lipoid nephrosis" loses its status as a disease, and is relegated to being a syndrome comprising clinical phenomena which may be both renal or extrarenal in origin.

Even as a clinical entity, "lipoid nephrosis" has been shown to lack the sharp differentiation from glomerulonephritis that its sponsors formerly contended. This has come about through the biological study of the disease. It was held that "lipoid nephrosis" differed from glomerluonephritis in two particulars, first that hypertension was lacking and, second, that "lipoid nephrosis" was not associated with renal insufficiency. A study of the biology of "lipoid nephrosis" has amply shown by adequate follow up that an appreciable number of such cases develop both hypertension and renal insufficiency.[3,9,14,15] This does not imply that a new malady has been superimposed, because at post-mortem the typical morphological evidences of glomerulonephritis were found. The presence or absence of hypertension is

*This case will shortly be reported by Gerber and Moschkowitz in a paper on "visceral thrombo-phlebitis migrans."

important in the differentiation between "lipoid nephrosis" and glomerulonephritis; but whether it is present throughout the course of every glomerulonephritis is an open question, because we are not always in a position to study every case throughout its life cycle. But that hypertension is lacking at some particular cross section of this cycle is a familiar observation. The same reasoning applies to the presence or absence of renal insufficiency. In the final analysis, these differentials are subject to a time factor.

Morbid Anatomy. The specificity of "lipoid nephrosis" as a distinct disease has been based on the paucity or even absence of the productive morphological changes within the glomeruli conventionally viewed as characteristic of glomerulonephritis. In view of the close clinical mimicry between "lipoid nephrosis" and the nephrotic form of glomerulonephritis, some have suspected that "lipoid nephrosis might be one of the anatomical results of a glomerulonephritis. There has been much controversy about the interpretation of the glomerular changes that have been observed in "lipoid nephrosis" and pathologists found it difficult to understand how a lesion like glomerulonephritis, so unmistakably of a productive nature, could evolve into a lesion in which the changes in the glomeruli were so minimal or even absent. Bell[1] revived the controversy in 1929 and by employing the histological technique of Mc Gregor he described in four cases of "lipoid nephrosis" a thickening of the basement capillary membrane and a varying increase in the number and size of the glomerular endothelial cells. These lesions he interpreted as evidences of a glomerulonephritis. Bell's conclusions have been criticised on the ground that none of his four cases appeared to be unalloyed instances of pure clinical "lipoid nephrosis." The entire problem depends upon whether our knowledge of the evolution of the morbid anatomy of acute glomerulonephritis is complete. We are well informed in the clinically progressive cases, whether or not associated with a "nephrotic component," but we are still unacquainted with the morphological appearance of such a kidney in apparently healed cases. Furthermore, clinicians have known of clinically established cases of acute glomerulonephritis that lose their hypertension and renal insufficiency and pass into a subacute phase in which the only clinical evidence of a renal disorder is a proteinuria of a considerable degree; in time, such patients eventually develop the classical clinical manifestations of a "lipoid nephrosis." The clinical continuity does not again permit us to say that a new disease has been superimposed. What lesions may we expect to find under such circumstances? Opportunities to observe such a sequence of events and a post-mortem examination come but rarely, and so we feel privileged to report such a case.

Case 2. (Adm. 461645). R. H., age 3 years, was first admitted to the Pediatric service (Dr. B. Schick) of the Mt. Sinai Hospital, December 3, 1939. She had been sick with fever and sore throat for a week, swelling of face and abdomen for 2 days, and red urine for 1 day. There was moderate swelling of face and legs. The temperature was 103° F. but returned to normal the next day. There was evidence of receding tonsillitis. The blood pressure was 140 systolic and 100 diastolic; the blood urea nitrogen was 8 mg. per 100 cc.; the serum protein was 5.1 gm. %, of which the albumin fraction was 3.8 gm. %. The urine contained albumin 2 plus, red blood cells and few casts. On December 5, it was noted there was no gross blood in the urine. On discharge, December 19, 1939, albumin had disappeared from the urine.

Second admission (March 12, 1940). Three weeks before admission generalized edema was noted. The blood pressure was 124 systolic and 90 diastolic; the

blood urea nitrogen 9 mg. per 100 cc.; the total serum protein 4.5 gm. %, of which the albumin fraction was 2.5 gm. %; and the cholesterol 550 mgm. per 100 cc. During her stay in the hospital the edema persisted, the urinary albumin was 3 plus, the cholesterol was high, on one occasion attaining 1050 mg. per 100 cc. The blood pressure remained about the same. The patient was discharged August 6, 1940.

Third admission (August 25, 1941). No clinical improvement was noted during her home stay. The blood pressure was 110 systolic and 85 diastolic. The serum protein was 3.3 gm. %, of which the albumin fraction was 1.5 gm. %. The blood chemistry was the same as on the last admission. The child had erysipelas twice. She died of a pneumococcic peritonitis on January 12, 1941. The urine always contained 4 plus albumin with a few red blood cells and rare casts. Two weeks before death the blood urea nitrogen was 28 mg. per 100 cc.

Necropsy (no. 11728). **Microscopic examination.** The renal architecture of the kidney seems not to be profoundly disturbed; however, throughout the cortex one sees small foci of tubular atrophy with increased stroma and frequently one sees the stroma widened with infiltration by lymphocytes with occasional polymorphonuclear leukocytes.

The proximal convoluted tubules are quite distended and contain a considerable amount of albumin. The epithelial cells generally show a good brush border and the cytoplasm is finely granular. The terminal portions of the convoluted tubules contains a large amount of pink granular material which is probably albumin. The

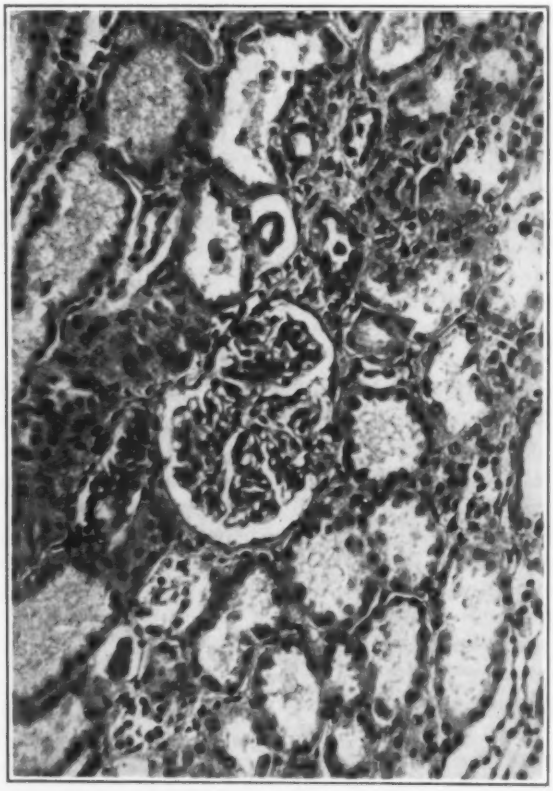

Fig. 2.—Kidney from Case 2, that clinically began as a glomerulonephritis and termed clinically as a "lipoid nephrosis," showing a glomerulus partially adherent to the glomerular capsule.

epithelium in such portions shows vacuolization. Glomeruli: A superficial examination of the glomeruli seems to indicate that they are not materially altered. However, if one examines more carefully, one finds certain changes affecting the majority. The lobulation of the tuft is exaggerated and the lobules appear rather plump. The basement membranes of the capillary loops are thick and there is fusion of such loops with each other and with the capsule. Some glomeruli show multiplication of the capsule epithelium. The Bowman's space contains only a small amount of albumin (Fig. 2).

Epicrisis. While not completely satisfying the criterion of a true anatomical "lipoid nephrosis" in that most of the glomeruli show minimal changes, the kidneys correspond closely to those described by such ardent sponsors of the disease specificity as Fahr[5] and Munk[13] even in regard to their focal distribution. In other respects the histological changes of the previous glomerulonephritis had completely resolved. These kidneys, in other words, might be regarded as instances of "lipoid nephrosis," provided we had not known that the patient had previously passed through a classical attack of glomerulonephritis. On his third admission, his hypertension had disappeared, so that had this patient been seen for the first time during his third admission, the diagnosis of "lipoid nephrosis" would have been justifiable.

The succeeding case is presented because the sequence of clinical events was the reverse of the preceding.

Case 3. S.M. (adm. 244959) male, aged 8, was admitted to the Pediatric service (Dr. B. Schick) of the Mt. Sinai Hospital for the first time on Nov. 20, 1921. He presented at that time a general anasarca of 6 weeks' duration with a pronounced proteinuria and casts. The blood pressure was 100 systolic and 80 diastolic, the blood urea nitrogen varied between 16 and 19.6 mg. per 100 cc. The serum protein was 4.2 gm. per 100 c.c. and the blood cholesterol was 682 mg. per 100 cc. The basal metabolic rate was minus 30%. The diagnosis of "lipoid nephrosis" was made. Six months later he returned with glandular swelling of the neck, an enlarged spleen, slight fever and a lymphocytosis. A diagnosis of infectious mononucleosis was made. The anasarca and the marked proteinuria was still present. The blood urea nitrogen was 14 mg. per 100 cc., the blood cholesterol 630 mg. per 100 cc., and the blood pressure was 105 systolic and 60 diastolic. His third admission occurred 15 months later for an upper respiratory infection. The blood pressure on this admission was 145–100 mm. Hg. The blood urea nitrogen was 30.8 mg. per 100 cc. The blood cholesterol was 356 mg. per 100 cc. About 9 months later he was again admitted. Two days previously he had abdominal pain with vomiting. Aside from the general anasarca he had signs of peritonitis. The blood culture showed a pneumococcus type iii. There was fever up to 103° F. for 3 days after admission. The signs of peritonitis disappeared, but he developed an abscess in the lumbar region which was incised. He remained in the hospital for over 5 months. The blood pressure varied between 90 and 124 systolic and 50 to 80 mm. Hg. diastolic. On discharge it was 100 systolic and 70 diastolic. The blood urea nitrogen was 30.8 mg. per 100 cc. on admission but thereafter it was normal. The blood cholesterol varied between 170 to 260 mg. per 100 cc. The proteinuria had diminished appreciably during his stay, and the anasarca disappeared. The basal metabolic rate was practically normal showing 33–35 calories per kilo of body weight. The fifth and last admission occurred about 5 months later (April 12, 1925) and about 3½ years after the first admission. Two days previously he had chills and high fever due to an extensive cellulitis of the thigh and abdominal wall. The blood culture showed pneumococci. There was general anasarca, a marked proteinuria and a blood cholesterol of 334 mg. per 100 cc. The blood pressure was 100 systolic and 60 diastolic. He died 3 days later.

Necropsy findings. Microscopically, there is diffuse tubular degeneration with

abundant fat droplets in the epithelium. In numerous places these degenerated cells have undergone calcification. In a very few areas, the capsule of Bowman is definitely thickened and the glomerular cusps are adherent. There are numerous areas of round cell infiltration of the cortex (Fig. 3).

Epicrisis. This patient's clinical manifestations at the first examination were those of a typical "lipoid nephrosis." Inasmuch as the reason for his entry was a generalized edema, the disease must have begun probably many months before. On his third admission, a definite hypertension was noted and the diagnosis of "lipoid nephrosis" was abandoned. A fluctuating but moderate systolic hypertension persisted until his last entry and was associated with a transient infection; a moderate azotemia developed which later subsided. In the final admission, following a pneumococcemia, the blood pressure returned to normal, the anasarca and proteinuria was pronounced, there was a slight azotemia. In view of the glomerular changes, however slight, one must conclude that this patient suffered from a glomerulonephritis from the onset. The glomerular changes we have described are reported by such advocates of "lipoid nephrosis" as Fahr[5] and Munk[13] as an anatomical entity and an integral part of the lesion of "lipoid nephrosis." However, inasmuch as the precise changes are observed in occasional glomeruli in otherwise unmistakable subacute and chronic glomeru-

Fig. 3.—Kidney from Case 3, that began clinically as a "lipoid nephrosis" and terminated as a glomerulonephritis showing round cell infiltration of the cortex and thickening of an occasional glomerular capsule.

lonephritis, it is fair to presume that this viewpoint is arbitrary.

These two cases of glomerulonephritis with minimal glomerular changes and masquerading clinically as "lipoid nephrosis" suggest the possibility that a glomerulonephritis may anatomically resolve, leaving the glomeruli intact. The following is such a case:

Case 4. (adm. 305675) S.L.T. male, aged 2½ years, was admitted to the Pediatric service of the Mt. Sinai Hospital (Dr. B. Schick) on August 14, 1929. There was swelling of the eyelids and face which began 3 months ago. The urine showed a marked proteinuria and some casts. The blood pressure was 100 systolic and 60 diastolic. The P.S.P. showed an excretion of 43% in two hours. The blood urea nitrogen was 10.0 mg. per 100 cc., the blood cholesterol was 346 mg. per 100 cc. The total blood protein on one determination was 7.08 gm. %, one week later it was 5.4 gm. % and a few days before death it was 3.55 gm. %. After 2 weeks the edema subsided. Four weeks later he developed a pneumococcus pneumonia followed by a peritonitis. He died 3 days later. The blood pressure was within the range of normal during most of his stay, but at times it reached 130–90 mm. Hg. The blood urea nitrogen levels remained within the range of normal the highest being 14.0 mg. per 100 cc.

Necropsy (no. 6909): **Microscopic examination.** The glomeruli are normal. The cytoplasm of the tubules is swollen and show numerous vacuoles. With the microscopic polaroscope many double refractile bodies are visible in the cytoplasm of the tubules and also in the interstitial cells of the kidney. With the fat stain, there are deposits mainly in the tubules and a few in the interstitial tissue (Fig. 4).

Fig. 4.—Glomerulus from Case 4, that clinically was a glomerular nephritis but anatomically the organ revealed a "lipoid nephrosis." The glomerular endothelium is swollen and filled with fat granules but there is no proliferation.

Epicrisis. In the past 25 years, this is the first of the only two cases of true or genuine anatomical "lipoid nephrosis" that have come to post-mortem examination in the Mt. Sinai Hospital. Even here the question arises whether this patient had a previous glomerulonephritis or not. If even a transient hypertension in the course of the illness of the slight degree mentioned above may be viewed as a distinguishing mark of a glomerulonephritis, we would be forced to conclude that an acute glomerulonephritis preceded the morphological picture of a "lipoid nephrosis." Nevertheless despite the

normal appearance of the glomeruli with our modern microscopic technique, their capillary membranes possessed a pronounced permeability for protein. The important light that this case throws upon the evolution of glomerulonephritis is this; that an acute glomerulonephritis may apparently resolve completely in the histological sense, although the clinical manifestations pursue their course.

Fig. 5.—Intact glomerulus from a man aged 43 who developed the typical clinical and anatomical manifestations of lipoid nephrosis, soon after a course of treatment for syphilis.

The second case of pure "lipoid nephrosis" is presented not only because hypertension was absent throughout the period of observation, but also because of the presumably syphilitic origin of the disease.

Case 6. (adm. 287343) A.M. male, aged 48, was admitted to the second medical service (Dr. B. S. Oppenheimer) of the Mt. Sinai Hospital January 18, 1928. Six and one half months prior to admission he had been given antiluetic treatment for a 4 plus Wassermann reaction. During this period his urine was albumin free. One week after the last mercury injection he developed sore gums and a generalized anasarca. The Wassermann test was now negative. His blood pressure was 100 systolic and 64 diastolic. The urine showed protein in large amounts, hyaline and granular casts and doubly refractive lipoid bodies. The blood urea nitrogen was 20.0 mg. per 100 cc., the cholesterol 600 mg. per 100 cc., and the total serum protein was 7.0 gms. %. The diagnosis of "lipoid nephrosis" was made and he was given vigorous antiluetic treatment with neosalvarsan and bismogenol. Despite this, the anasarca became progressive. To relieve the extreme edema of the legs, Southey tubes were inserted. Eventually he developed erysipelas and

he died a little less than a month after admission.

Necropsy (no. 6088): **Microscopic examination.** The glomeruli are entirely normal with the exception of a sporadic fibrous glomerulus. In not a single glomerulus is there any proliferation of the capsular or capillary endothelium, and the capillaries are everywhere patent. The capillary walls are thin. The epithelium of the convoluted tubules is swollen, contains large granules, and there are many doubly refractive fat droplets particularly near the basement membrane. In occasional tubules, honeycombed desquamated epithelial cells lie within the lumen (Figs. 5 and 6).

Fig. 6.—Tubules from same case as Fig. 5, showing basal vacuolization of the protoplasm and hyaline droplet degeneration toward the lumen.

Epicrisis. It is difficult to appraise this case. The absence of albuminuria only a few weeks before his admission renders a previous glomerulonephritis most unlikely, but the fact that a profound albuminuria appeared shortly after extensive mercurial stomatitis suggests the necrotizing nephrosis of mercury poisoning, rendering the capsules of Bowman permeable to protein. There is no factual evidence that syphilis is the cause of a "lipoid nephrosis."

Comment. It is apparent that our knowledge of the histomorphological evolution of acute glomerulonephritis requires revision. Apparently, in some instances, especially in children, the productive changes are so slight that only minimal glomerular changes are produced. In other and much rarer instances the productive changes appear to disappear completely. In the latter case, the anatomical picture of a true or genuine "lipoid nephrosis" results; when minimal lesions of the glomerulus persist we derive what Bell[2] calls the "mixed" form. One merges imperceptibly

tibly into the other and the end result is quantitative and not qualitative. Pathologists are not in the habit of visualizing glomerulonephritis in this light. The factor or factors which determine the intensity of the glomerular lesion are entirely unknown. These biological sports in the evolution of glomerulonephritis do not permit us to predict the morphological findings from the clinical phenomena, except in the broadest way. We can often predict the amount of lipoid infiltration in the renal parenchyma from the level and duration of the hypercholesterinemia. The extent and maturity of renal damage is only one of the factors in producing renal insufficiency, since this is conditioned by extra-renal factors, notably cardiac failure from an associated hypertension, or a concomitant febrile disorder. According to Bell[2] hypertension does not develop unless the basement membrane of the capillaries become so thick that they become narrowed; and the blood flow is decreased. That this mechanism does not always maintain is shown by the cases with hypertension we have described in which there was either no thickening of the basement membrane, or when it was present, the number of affected glomeruli were so small that the thickening could hardly cause renal ischemia. The cause of the hypertension in glomerulonephritis remains problematical.

Summary. The term "nephrosis" has been so modified by subsequent students of the malady from its original connotation, that when it is employed one should demand a definition.

The fundamental clinical phenomena of "lipoid nephrosis" are here reviewed and their genesis outlined. The primary factor is a prolonged hypoproteinemia. The hypoproteinemia is the result of a persistent proteinuria consequent to an increased permeability of the glomerular capillary walls, which is not always explainable histologically with our current technical methods. The hypoproteinemia, and especially, hypoalbuminemia, is responsible for the edema and anasarca and for the low protein content of the exudate. In addition, the hypoproteinemia is probably indirectly responsible for the low basal metabolic rate by creating an edema which acts as a suit of clothes preventing the dissipation of heat. This explanation is based on our demonstration that integumentary thickenings of whatever nature are usually accompanied by a low basal metabolic rate. The lipemia represents in all probability a compensatory phenomenon.

Evidence has been submitted to show that anatomical "lipoid nephrosis" represents nearly always one of the biological progressions of a glomerulonephritis, in which the conventional productive changes have either disappeared or have not developed. In other instances, it may be the result of extrarenal factors in which a hypoproteinemia ensues.

Clinical and anatomical "lipoid nephrosis" are by no means synonymous. In the last analysis, "nephrosis" is not a disease in the sense that it has a consistent background in either morbid anatomy or etiology. Instead of employing a generic term to cover a multitude of unrelated morphological backgrounds, accuracy of thought would be promoted by ascribing the best available descriptive term for each renal disorder.

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THE CLINICAL USES OF INTRAVENOUS DIPHENHYDRAMINE HYDROCHLORIDE (Benadryl Hydrochloride)

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Reports on diphenhydramine hydrochloride (benadryl hydrochloride) are in general agreement as to the value of this drug in certain allergic diseases, such as hay fever and urticaria. There is also general agreement as to its lack of efficacy in most patients with bronchial asthma. These 3 allergic conditions comprise the largest percentage of cases in which the anti-histaminic drugs have been used. Most reports include a small number of other conditions, either allergic or questionably so. Some conclusions have been drawn as to the value of the compound used from the results obtained in a small group of patients.

One of the difficulties present in the attempt to evaluate any drug in the treatment of a specific disease is the time interval which must elapse between the administration of the medication and the time the effects are first observed. If the disease is one in which subjective symptoms wax and wane rapidly, it may be impossible to determine the effect of a particular medication.

The purpose of this study is to evaluate the use of an intravenous solution of benadryl* in the treatment of conditions generally accepted as being allergic as well as in conditions which are questionably allergic in nature. If a medication brings relief within a few minutes after it is given, the possibility that the relief is directly related to the medication is greater than if there is a time interval of 30 to 60 minutes before relief is obtained. It was felt that the results would be of therapeutic importance and might aid in evaluating the drug in conditions in which its efficacy is questionable.

Material and Methods. Thirty-nine patients were treated with easily evaluated symptoms of a possible allergic nature. An intravenous solution of benadryl was used which contained 10 mg. per cc. It has been our practice to use a dilution of approximately 10 mg. per 30 cc. of normal saline. Our usual dose had been 30 mg. of benadryl given by a continuous intravenous drip, taking from 7 to 12 minutes to complete the procedure. Doses of 10 to 50 mg. have been used in appropriate dilutions. The results of the therapeutic trials are listed in Table 1.

Results. Urticaria. Twenty-one patients with urticaria were treated. Nineteen of these experienced complete relief of the pruritus immediately. It was interesting to see that the relief of symptoms, if it occurred, followed a certain rather definite pattern. Many patients first noticed diminution in the pruritus when as little as 10 mg. of the benadryl had been received. The relief was centrifugal in nature, first being experienced on the trunk and back,

* Supplied through the courtesy of Dr. E. A. Sharp; Parke Davis & Co.

then progressing down the extremities until the final points of discomfort were usually the hands and feet. These patients were very much aware of their discomfort due to the pruritus. As this diminished, many of them then complained of a burning sensation. It was felt that this burning sensation was due to the local irritation from scratching and rubbing. This sensation disappeared by the end of the infusion. The wheals also changed as the treatment was being given. In the fair-skinned patient, the red wheal blanched from the center outward so that at times the wheal would become a raised area comprised of a red rim around a blanched center. The size of the wheal did not usually change immediately but would gradually disappear over a period of about 1 hour.

TABLE 1.

CLINICAL RESULTS OF INTRAVENOUS BENADRYL HYDROCHLORIDE IN 39 PATIENTS

Diagnosis	No. of Cases	Improved	Not Improved
Urticaria	21	19	2
Asthma	3	1	2
Vasomotor Rhinitis	2	2	
Pruritus with—			
Poison Ivy	4	4	
Jaundice	1		1
Neurodermatitis	2	1	1
Miscellaneous—			
Allergic Arthritis	1	1	
Gonorrheal Arthritis	1		1
Tabetic Crises	1		1
Unilateral Headache	1		1
Dysmenorrhea	1		1
	39	29	10

In some patients the period of relief was only 3 or 4 hours. In others no further medication was required for 6 to 8 hours. All patients relieved by the intravenous benadryl in whom a recurrence of the itching occurred, obtained relief by the use of the drug orally. Three of the patients with urticaria who had relief did not have a recurrence of the pruritus after the initial intravenous dose was given and no further oral therapy was necessary.

It is of interest to note that the 2 patients who did not respond to intravenous benadryl were both patients whose urticaria followed the use of penicillin in wax and oil. It has been our experience that those patients, who have responded, usually have started to do so by the time they have received 10 to 15 mg. o fbenadryl. Our feeling has been that if the patients did not respond to 30 mg., they would not respond to any dose and treatment with an anti-histaminic agent was then abandoned. This was our procedure in the 2 cases of urticaria which did not respond to intravenous benadryl. However, one of our more recent patients was one who developed angioneurotic edema of the face and lips following antiluetic therapy with penicillin, bismuth and mapharsen. He was given 30 mg. of intravenous benadryl with no change in the angioneurotic edema and little change in the associated pruritus. Following this he was then put on 100 mg. of oral benadryl every 3 hours, with marked relief of symptoms and disappearance of the edema. The response of this patient to oral medication after failure of the intravenous drug has made us realize that in some patients our arbitrarily chosen dose of 30 mg. of the intravenous solution may be insufficient. Any patients who do not obtain relief from 30 mg. intravenously

probably should be given a larger dose before the drug is definitely considered to be ineffective.

Asthma. Three patients with severe acute attacks of bronchial asthma were treated with intravenous benadryl, 2 receiving 40 mg. of the solution and 1 receiving 30 mg. In 2 cases there was no appreciable change in the patient's condition; 1 received immediate objective relief. All of these patients had received various other forms of therapy previous to the use of benadryl. There have been reports in which benadryl has proved of value in the treatment of asthmatics but generally the reports have been discouraging.

Miscellaneous. Four patients with contact dermatitis (poison ivy) were given intravenous benadryl. All of these patients had immediate cessation of the pruritus. One, after being relieved of his pruritus by an injection of intravenous benadryl, was put on a maintenance dose of 50 mg. orally every 4 hours. He experienced no relief from this medication and the dosage was increased until the patient was receiving 100 mg. every 2 hours. No relief was obtained with these large doses. This is the only patient in our series who was relieved by the intravenous preparation but not by the oral drug. The only explanation felt plausible is that absorption of the drug from the gastrointestinal tract was impaired.

We have recently reported[1] the use of benadryl in 14 cases of poison ivy dermatitis with complete relief of itching in 12 cases and moderate relief in 2. Some authors have reported good results, others poor results in the relief of the pruritus of poison ivy dermatitis by benadryl. It is our opinion that the use of intravenous benadryl is the most objective method of determining the value of the drug in this and similar conditions.

One patient with tabetic crises was not benefited. Neither were 2 other patients, one of whom had a severe unilateral headache with certain migrainous features and the other who had a chronic gonorrheal arthritis with a painful knee joint. The last 3 patients were included because of the possibility that there might have been an allergic factor in the production of their symptoms.

One patient with pruritus associated with chickenpox was given intravenous benadryl with marked relief from the itching. She was then maintained on oral benadryl with relief. Several other patients with chickenpox also received marked relief from the use of oral benadryl.

Two patients with neurodermatitis were treated. One experienced no relief from the intravenous therapy while the other had marked relief. The patient who was not relieved was given very large doses of oral benadryl without effect. The patient who was relieved was maintained on the oral medication with marked relief from itching and clearing of the skin lesions. Two patients with vasomotor rhinitis experienced complete relief after the administration of intravenous benadryl. One patient with an allergic arthritis of a palindromic nature also was relieved. One patient who had pruritus associated with jaundice was not relieved. One patient with severe dysmenorrhea was not benefitted.

Discussion. The use of an intravenous preparation of benadryl has not been stressed in many reports. Some authors have found certain specific advantages in using the intravenous mode of administration. McElin and Horton[2] attempted to inhibit the rise of histamine induced gastric acidity in patients with multiple sclerosis by use of intravenous benadryl. They felt that there is suggestive evidence that in some instances the curve of gastric acidity is

altered in patients with multiple sclerosis. Reinstein and McGavack[8] found that oral benadryl had no effect on the glucose tolerance, whereas when given intravenously in 30 mg. doses, benadryl seemed to increase sugar tolerance. Moersch *et al.*[9] studied the gastric secretory response of patients given intravenous benadryl. It had been shown previously that successive equal subcutaneous injections of histamine produced almost identical curves of gastric acid response.[9] This served as a basis for what the authors designated the "double histamine test." After determining if in the original test the curves were similar, a tested material was then introduced between the 1st and 2nd curve. If there is a change in the 2nd curve it is felt that the introduced material may be responsible. After the concentration of hydrochloric acid and the total volume of gastric juice was obtained following subcutaneous histamine, intravenous histamine, and a test meal, in 3 groups of patients, these patients were then given an identical test coupled with the use of intravenous benadryl. There was no material difference found in the volume of gastric content nor in the concentration of free hydrochloric acid after the administration of intravenous benadryl.

McElin and Horton[3] report the use of intravenous benadryl in 26 patients. In urticaria their results were good. One patient with dysmenorrhea was not benefitted. Their results in treatment of patients with hay fever and vasomotor rhinitis were good. In 1 case of acute bronchial asthma intravenous benadryl was tried on 3 occasions without relief. In 3 cases of histamine cephalgia, typical attacks were provoked by giving histamine subcutaneously. As soon as a typical attack had developed, intravenous injection of 60 mg. of benadryl per 100 cc. of physiological saline solution was begun at about 120 drops per minute. On all 3 occasions, relief was obtained promptly; in one, definite and complete relief was obtained in 30 seconds. However, in 8 cases of histamine cephalgia the oral use of the drug seemed to be of only limited value.

Toxic Effects. McElin and Horton[3] suggested early in the study of the use of benadryl that the intravenous method of administration was of value in the clinical investigation of the drug. They used doses of 10 to 120 mg. by the continuous drip method. Routinely they recommended the use of 60 mg. in 100 cc. of normal saline solution With this method they encountered no evidence of acute toxicity. Dizziness, sleepiness, and dry mouth were the significant side reactions. It was noted that dizziness was present in every patient when the sitting position was assumed at the end of the injection. These symptoms were of short duration. McGavack *et al.*[4] reported reactions in 3 of 10 subjects given intravenous benadryl. One patient was given 20 mg. and the other two 30 mg. each, of the drug. The reaction in one patient consisted of weakness, headache, "sea-sickness," and drowsiness, all associated with extreme pallor. No estimation of the blood pressure was given. The 2nd patient complained of dizziness with a sensation of falling to the left which lasted about 1 hour. The 3rd patient developed a severe chill associated with sweating, headache, low back pain and a slight decrease in temperature but with no change in either pulse rate or blood pressure. In this article no mention was made of the dilution factor used. However, one of the authors[6] states that his practice has been to inject the intravenous benadryl undiluted, usually taking from 30 to 90 seconds for the injection. This may account for the high percentage of reactions obtained.

As mentioned, our practice has been to inject 30 mg. in about 75 to 100 cc.

of normal saline by continuous drip, taking from 7 to 12 minutes to complete the injection. Of our 39 patients, 8 experienced side effects. Two were both dizzy and sleepy, 2 were dizzy and 2 were sleepy. One patient had a chilly sensation followed by a mild chill immediately following cessation of the injection. This wore off in about 2 minutes. Another patient immediately following the injection felt sleepy. However, about 90 minutes after the treatment he suddenly developed bilateral low back pain, headache and a shaking chill which lasted about 20 minutes. When this wore off he had no further reactions. In all of these patients, the side effects wore off very quickly. It is felt that the dosage, dilution factor, and speed of administration were responsible for the lack of more toxic effects. That there is a wide safety factor between the therapeutic and toxic doses can be seen from the large doses that have been used. Moersch *et al.*[6] report the use of 200 mg. of benadryl in 200 cc. of normal saline by continuous drip at the rate of 35 to 40 drops per minute. Toxic effects are not mentioned. One of the authors states that no serious toxic effects were noted after use of large doses.[7] McGavack[5] states that he has given as high as 100 mg. intravenously undiluted with no serious side effects. From the results we have obtained, we feel that a usual dose of 30 mg. is sufficient to produce a therapeutic result. If that dose is unsuccessful, then the use of a larger dose is justified. If there is no response to the intravenous drug it is felt that the oral form of therapy is not indicated.

That intravenous benadryl has a certain therapeutic value is unquestioned. In our opinion the use of this type of therapy is of even greater aid in permitting the quick evaluation of the efficacy of the drug in any particular condition in which the value of the medication is doubted. If relief is obtained with the intravenous preparation, then the oral method of administration should also be effective if large enough doses are given. Frequently the drug has been felt to be ineffective, when in reality it was not being used properly. On several occasions it was found that patients were receiving small amounts of the drug by mouth with little or no relief. These patients were then given intravenous benadryl with immediate relief of symptoms Larger doses were recommended by mouth and the patients then obtained relief.

Summary. Thirty-nine patients were treated with an intravenous preparation of benadryl. The results obtained were similar to those obtained in the use of the oral preparation. The various uses to which intravenous benadryl has been put are reviewed. A dosage and dilution of intravenous benadryl has been recommended. Toxic effects have been discussed and their relation to dosage, dilution and speed of administration have been described. It is felt that one of the most useful purposes of intravenous benadryl is to aid in the immediate evaluation of the drug in any condition in which its value is uncertain.

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THE EFFECTS OF CERTAIN DIHYDROGENATED ALKALOIDS OF ERGOT IN HYPERTENSIVE PATIENTS*

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CLINICAL experience with surgery of the sympathetic nervous system has stimulated the search for chemical agents that will effectively inhibit functions of the sympathetic nervous system, particularly vasoconstriction. Among the compounds found to have sympatholytic and vasodilator properties are the tetraethylammonium salts[7], dibenamine[9], and pentaquine.[6] None of these agents, however, has proved to be of practical value in the treatment of essential hypertension.

An additional group of sympatholytic agents has been available in the naturally occurring alkaloids of ergot.[4,11] However, these substances do not possess significant vasodilator properties, presumably because of their direct stimulating action on smooth muscle including that of the blood vessels[11]. As a result, they have found no use as therapeutic agents in peripheral vascular disease or in essential hypertension.

Recently Stoll and Hofmann have prepared dihydrogenated derivatives of the ergotoxine group of alkaloids[12] which exhibit marked sympatholytic and adrenolytic properties in animals with only slight direct stimulating effects on smooth muscle[11]. These compounds are less toxic in animals than the naturally occurring derivatives of ergotoxine and one of them, dihydroergocornine, when administered intravenously has been found by Bluntschli and Goetz[2] to lower the blood pressure of hypertensive patients. The present communication confirms and enlarges the experience of these workers on the clinical and pharmacological effects of the dihydrogenated derivatives of ergotoxine in normal and hypertensive man.

Materials and Methods. The 3 compounds tested were dihydroergocornine (DHO 180), dihydroergokryptine (DHK 135) and dihydroergocristine (DCS 190). Fifteen patients received dihydroergocornine, 7 received dihydroergocristine, 8 were administered dihydroergokryptine, while 4 hospitalized patients received each of the 3 drugs at intervals of 3 or more days apart. The drugs were administered usually intravenously, and occasionally orally to hospitalized and ambulatory patients with hypertension, and also to normotensive subjects. The mean arterial pressure was calculated as half the sum of the systolic and diastolic

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blood pressure, which unless otherwise stated was taken with an arm cuff and mercury manometer. Control blood pressures were obtained for a period of ½ hour prior to the administration of the drug.

Results. Effect on Blood Pressure and Pulse Rate. The hypotensive response to the administration of these dihydrogenated alkaloids of ergot was extremely variable in different patients (Table 1). All gradations of response occurred from insignificant to marked reductions in blood pressure. For example, after an intravenous injection of 0.5 mg. of dihydroergocornine in a reactive subject (Figure 1) the blood pressure decreased definitely within 1 minute and markedly within 10 minutes. During the early period after injection in such a patient, his pulse rate was unaffected and he had no symptoms, unless allowed to stand, whereupon he developed a further fall of blood pressure soon followed by bradycardia and collapse (Figures 1 and 2).

Following an intravenous injection of any of these compounds in a reactive subject the blood pressure usually fell progressively for 10 to 30 minutes to normotensive levels, and thereafter rose slowly to control values over a period of 1 to 24 hours or longer (Figure 1). Other subjects exhibited no reduction of arterial pressure or only slight hypotensive effects which lasted for 10 minutes or less. Similarly, the presence and the degree of postural hypotension varied in different individuals, but in general, was most marked in those who exhibited the greatest reduction of blood pressure in the supine position. Most commonly 5 to 20 minutes following the administration of these drugs a reduction in cardiac rate occurred, sometimes accompanied by the side effects described below. A summary of the effects on blood pressure and pulse rate is given in Table I.

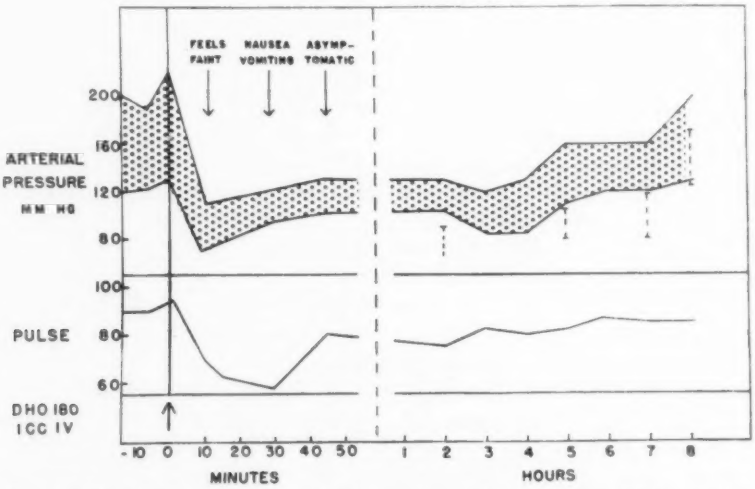

FIG. 1.—The typical response to the intravenous administration of 0.5 mg. (1 cc.) of dihydroergocornine (R. P., female, aged 23, with essential hypertension). The short vertical broken lines on the right half of the chart indicate blood pressure recordings made with the patient in the erect position.

Of the available compounds studied, dihydroergocornine and dihydroergokryptine exhibited the greatest hypotensive activity (Tables 1 and 2). In

the supine position 8 of the 15 patients tested with dihydroergocornine exhibited a fall in blood pressure greater than 20 points systolic and 15 points diastolic, while 10 developed postural hypotension. The intravenous dose varied from 0.25 to 1.0 mg. When administered orally this dose produced little effect until it was increased to 4 to 8 mg. except in 2 patients, who responded to as little as 2 mg. Following an oral dose of 8 to 10 mg., 5 of 7 patients developed a significant reduction in resting blood pressure, while 2 of these 5 also exhibited postural hypotension and collapse. In only 2 of the 5 patients was the reduction in blood pressure in the supine position as great after 10 mg. administered by mouth as it was after 0.5 mg. administered in-

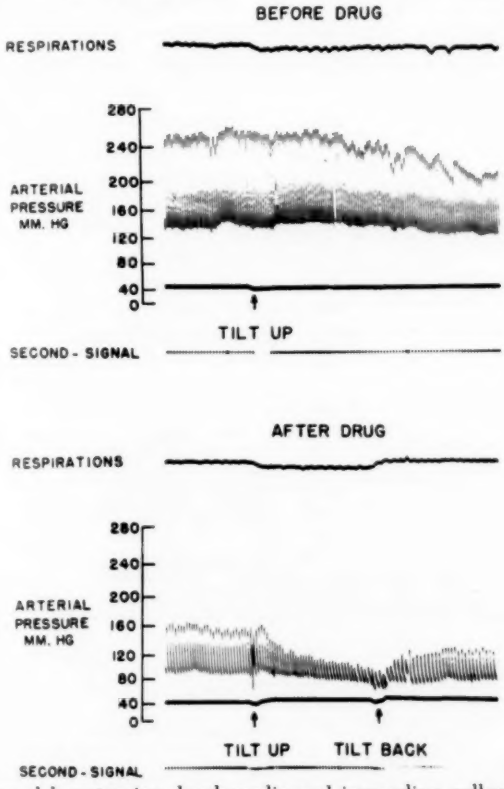

FIG. 2.—Postural hypotension, bradycardia and impending collapse (lower record) following the intravenous administration of 0.5 mg. of dihydroergocornine (K. M., female, aged 52). In the respiratory tracing inspiration is down. Arterial pressure was recorded from the brachial artery with a Hamilton manometer. The patient was lying on a table that at the arrow was tilted upright to an angle of 75°. Note that in the control period (upper record) she was able to stand for over a minute without the development of significant hypotension. After dihydroergocornine impending collapse occurred in 45 seconds following the tilt to the upright position.

TABLE 1.—SUMMARY OF THE EFFECTS OF THE 3 DIHYDROGENATED ALKALOIDS OF ERGOT ON THE BLOOD PRESSURE AND PULSE RATE AND THE INCIDENCE OF NAUSEA AND VOMITING

Drug	Number of Patients	Dose Intravenously Mgm.		Reduction in Mean Arterial Pressure Per Cent			Reduction in Pulse Rate Per Cent		No. of Patients Experiencing Side Effects	
		Mean	Range	Mean	Range	Standard Deviation	Mean	Range	Nausea	Vomiting
Dihydroergocornine	15	0.5	0.25-1.0	18	0-41	12	16	0-33	4	2
Dihydroergocristine	7	0.8	0.5-1.5	8	0-15	6	6	0-18	1	0
Dihydroergokryptine	8	1.2	0.5-1.5	13	0-20	5	14	0-24	2	1

travenously. These data suggest, therefore, that to achieve a comparable effect by oral administration approximately 10 to 20 times the effective intravenous dose usually must be given. In addition to the hypotensive response, 4 of the 7 patients exhibited a reduction in pulse rate of from 10 to 20 beats per minute, and four developed nasal stuffiness. The hypotension, bradycardia and nasal stuffiness appeared 1 to 2 hours after the oral administration of the drug and lasted 1 to 12 hours.

TABLE 2.—A COMPARISON OF THE HYPOTENSIVE EFFECT OF THE 3 DIHYDROGENATED ALKALOIDS OF ERGOT IN 4 PATIENTS WITH ESSENTIAL HYPERTENSION.

Patient	Drug	Dose Intravenously Mgm.	Reduction in Mean Arterial Pressure %
M.C.	Dihydroergocornine	0.5	28
	Dihydroergocristine	1.5	15
	Dihydroergokryptine	0.5	14
M.G.	Dihydroergocornine	0.25	19
	Dihydroergocristine	0.75	6
	Dihydroergokryptine	1.5	11
J.D.	Dihydroergocornine	0.5	5
	Dihydroergocristine	0.5	3
	Dihydroergokryptine	0.5	13
M.N.	Dihydroergocornine	0.5	6
	Dihydroergocristine	0.5	8
	Dihydroergokryptine	0.5	8

SIDE EFFECTS. No serious toxic reactions were noted. Some degree of nasal stuffiness due to congestion of the nasal mucosa was present in almost every case. This could be successfully combated by the local application of 0.25% solution of aqueous neosynephrin. Visual accommodation was unimpaired. Nausea occurred in 7 of 30 patients

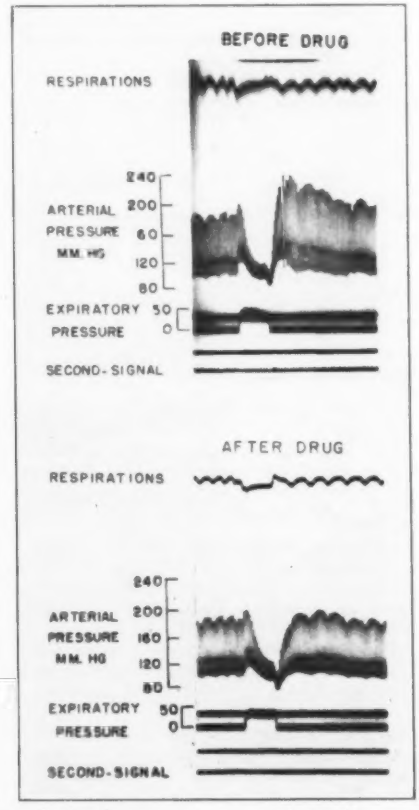

FIG. 3.—Inhibition of the hypertensive overshoot (lower record) following the Valsalva maneuver (R. S., female, aged 46, with essential hypertension). In the Valsalva maneuver the patient inspired deeply and exhaled for 10 seconds with maximal force against a fixed resistance. Other notations as in Fig. 2.

studied and in 3 of the 7 was followed by vomiting. These effects, often accompanied by sensations of faintness and giddiness, occurred during the period of bradycardia. It is worthy of note that the presence of side reactions was not related necessarily to the development of hypotension. For example, one patient exhibited a reduction of blood pressure from 245/128 to 150/80 with no side reactions of any kind except

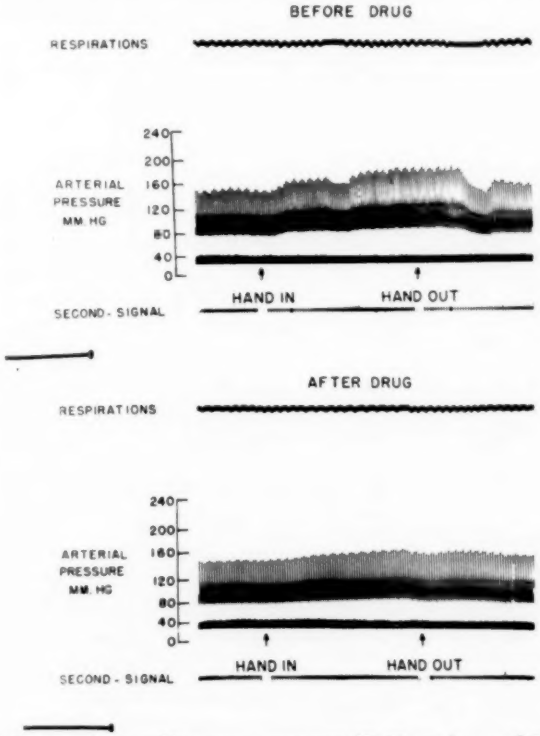

FIG. 4.—Inhibition of the cold pressor responses (C. T., male, aged 52, with essential hypertension following the intravenous injection of 0.5 mg. of dihydroergocornine). Other notations as in Fig. 2.

for the development of postural hypotension; while other patients without hypotension developed nausea and vomiting.

MECHANISM OF ACTION. The sympatholytic properties of these agents were demonstrated by the following effects.

(1) *The development of postural hypotension.* This, unlike the postural response seen within the first few months after lumbodorsal splanchnicectomy or that observed after such drugs as sodium nitrite or tetraethylammonium bromide was not accompanied by a significant increase in pulse rate. Immediately after the patient assumed the erect position the blood pressure frequently was maintained for a brief period only to fall over the succeeding several minutes. Collapse began with yawning or nausea, followed by faintness, sweating, pallor and bradycardia. Postural hypotension occurred in normotensive as well as hypertensive individuals.

(2) *Diminution in vasopressor response to blood-pressure-lowering procedures.* After dihydroergocornine the hypertensive overshoots which normally occur after the Valsalva maneuver (Fig.

ure 3), and the tilt-back from the upright to the supine position[14], were inhibited. This effect was identical with that observed after surgical splanchnicectomy[14] or the administration of certain other sympatholytic agents[15].

(3) *Reduction of the cold pressor response* (Fig. 4).

(4) *Diminution of digital reflex vasoconstrictor responses both to "noxious" stimuli and to body cooling.* This had no significant change in blood pressure. A similar inhibition of these reflexes was also observed in several normotensive individuals following the administration of dihydroergocornine.

(5) *A reduced hypotensive response to the drug in the same patient studied after as compared with before lumbo-dorsal splanchnicectomy.* Thus, the same dose in 3 patients produced an average reduction of 6% of mean arte-

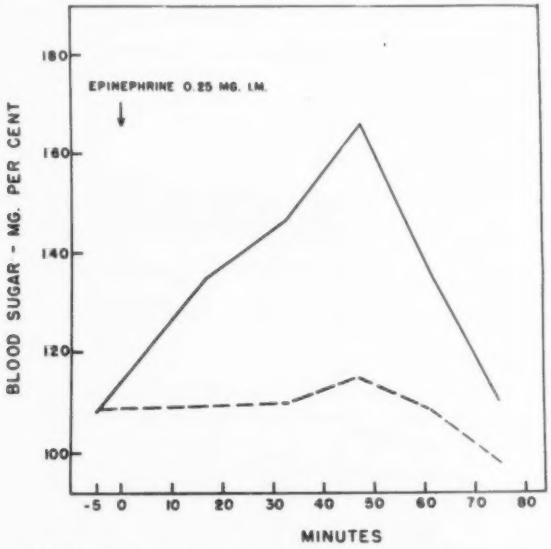

FIG. 5.—The blocking of hyperglycemic response to the intramuscular injection of 0.25 mgm. of epinephrine (J. S., male, aged 32, with a diagnosis of latent syphilis under treatment with penicillin). Normal diet; tests carried out in the postabsorptive basal state. In the 2d test, 2 days following the control test, 15 minutes prior to the injection of epinephrine, 1.0 mg. of dihydroergokryptine was administered intravenously, and immediately following the injection of adrenalin an additional 0.5 mg. of dihydroergokryptine was given by the same route. Another such test on a different patient gave similar results.

effect measured by digital plethysmography[3] and/or cutaneous thermometry[13] varied in amount from slight to almost complete suppression of sympathetic reflex vasoconstrictions in the fingers and toes. However, it bore no relation to the degree of hypotension. Thus, the reflex vasoconstrictions were only slightly inhibited in two hypertensive patients who exhibited marked reductions of resting arterial pressure, while they were almost completely abolished in two other patients who

rial pressure after lumbodorsal splanchnicectomy as compared to a 14% reduction prior to operation. By contrast, the drug produced the same degree of slowing of cardiac rate before and after lumbodorsal splanchnicectomy. Further, the tachycardia which otherwise occurred in the erect position after splanchnicectomy was inhibited by the administration of dihydroergocornine.

The adrenolytic properties of dihydroergokryptine were clearly shown by the inhibition in 2 subjects of the hy-

perglycemic response to the injection of epinephrine (Figure 5). The inhibition of the pressor response to epinephrine was less readily demonstrated. However, by using doses of from 1.0 to 1.5 mg. of dihydroergokryptine and by administering a minimal effective dose of epinephrine by constant intravenous drip in dilute solution, an adrenolytic effect on the blood pressure response could be demonstrated. Occasionally there was also inhibition of the tachycardia and mydriasis which ordinarily follows the injection of epinephrine.

In addition to the sympatholytic and adrenolytic actions noted above after any of these agents there were evidences of vagotonic effects including nausea, vomiting and bradycardia. These effects may have been due to unopposed vagal action rather than to direct vagal stimulation. The bradycardia, but not the hypotension, could be abolished by atropine. In contrast to the early appearance of signs of sympathetic inhibition, evidences of vagal stimulation were usually delayed until 10 to 20 minutes after the intravenous injection of the drug.

Dihydroergocornine apparently increased the tendency to collapse from venous pooling. Following administration of the drug postural hypotension and collapse were frequent, but could be prevented by the application of a tight abdominal binder and elastic stockings. Similarly collapse often was produced in the supine position after DHO 180 by the inflation of venous congesting cuffs high on the extremities for several minutes, when it could not be so produced before the drug.

Discussion. Although these dihydrogenated derivatives of ergot bear certain resemblances to other sympatholytic agents, their action is not identical with any of them. For example, in animals the ergot alkaloids have been shown to produce a central blockade of sympathetic reflexes[11]. This effect as well as the absence of significant tachycardia during the period of postural hypotension resembles that of pamaquine and pentaquine.[6,8,10] The ergot alkaloids differ from these latter agents, however, in that they also exhibit adrenolytic properties.

The selective adrenolytic, sympatholytic and vagotonic properties of the dihydrogenated ergotoxine compounds are in marked contrast to the indiscriminate blockade of all autonomic ganglia produced by the tetraethylammonium salts.[1] On the other hand their adrenolytic and sympatholytic properties suggest a similarity of action to that of dibenamine[9] and to Fourneau compound 883F[5]. However, the available evidence indicates that dihydroergocornine acts centrally[11] whereas dibenamine and Fourneau compound 883F are said to act peripherally.

One of the most striking features of dihydroergocornine in therapeutic doses was the marked variability of its hypotensive effect in different individuals. Its hypotensive action appeared to be related more to individual susceptibility than to size of dose as based on height, weight or age. Thus, increasing the dosage did not enhance the hypotension in certain patients who showed a poor response to standard amounts of the drug. The variability of action applied not only to the hypotension, but also to the other sympatholytic effects. Similar variability has been noted with other sympatholytic agents such as pentaquine[6] and tetraethylammonium bromide[7].

Bluntschli and Goetz[2] observed that parenteral doses of 0.1 to 0.3 mg. of dihydroergocornine had a greater hypotensive effect and a lesser incidence of side reactions than the larger dose of 0.5 mg. used in most of the cases in the present study. Increasing the dose beyond 0.5 mg. did not increase the hypotensive response in our series, whereas it did increase the incidence of side

effects. The question of dosage required to obtain optimum therapeutic (hypotensive) effects with minimum side reactions requires further investigation.

The search for compounds to produce a "chemical sympathectomy" as yet has not yielded a drug of practical therapeutic value in the treatment of patients with essential hypertension. Such an agent should be nontoxic in therapeutic doses; it should have a sufficiently long duration of action so that the patient may obtain his sleep, and ideally, it should be effective by mouth. In several respects dihydroergocornine fulfills these criteria. It is relatively nontoxic in therapeutic doses, and in selected cases, it reduces blood pressure in sufficient magnitude and duration to warrant additional clinical trial. However, in most patients the effective oral dose is so large that, for the present, this route of administration is neither practical nor economically feasible. The most serious limitations to its clinical use are the development of side reactions in some patients and the absence of significant hypotensive effects in others. In addition, the production of postural hypotension, which the drug has in common with all other sympatholytic agents, imposes a hardship on the patient. Definitive evaluation of its clinical usefulness must await long term studies in selected cases who exhibit a satisfactory hypotensive response to oral administration. The possibility of using dihydroergocornine as a test agent in predicting the outcome of splanchnicectomy is under investigation at present.

Summary and Conclusions. 1. Three new dihydrogenated alkaloids of ergot have been found to lower the blood pressure of a significant percentage of hypertensive patients following intravenous injection. The most effective agents in the group were dihydroergocornine and dihydroergokryptine. The degree and duration of hypotensive activity were extremely variable in different subjects.

2. These drugs have been shown to exert sympatholytic, adrenolytic and vagotonic properties:

a) Sympatholytic actions included the production of postural hypotension, the inhibition of hypertensive overshoots following depressor stimuli, diminution of reflex sympathetic vasoconstriction in the digits, and moderation of the cold pressor response. In addition the drug had a reduced hypotensive action following lumbodorsal splanchnicectomy.

b) Adrenolytic activity of dihydroergokryptine was demonstrated by inhibition of the hyperglycemic response to epinephrine, and under proper experimental conditions diminution of the pressor response, tachycardia and mydriasis, following epinephrine.

c) Evidence of vagal stimulation or of unopposed vagal activity was manifested by bradycardia and in some cases by nausea and vomiting.

3. No serious toxic reactions were observed. Nasal stuffiness occurred in almost every case. With the dosage used the other side effects, notably nausea, vomiting and faintness occurred in approximately 25% of the patients tested.

4. In selected cases dihydroergocornine was effective by the oral route usually in doses approximately 10 to 20 times greater than the effective intravenous dose.

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THE IMMEDIATE SEQUELÆ OF MYOCARDIAL INFARCTION
THEIR RELATION TO THE PROGNOSIS

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In spite of the marked upsurge of optimism in the evaluation of coronary artery disease, myocardial infarction remains one of the most unpredictable entities in clinical medicine. The reason for this is the multiplicity of factors influencing its course and immediate prognosis, for in addition to the actual derangement of the circulation caused by myocardial infarction, the course of the disease is often altered by secondary complications.

The immediate prognosis of acute myocardial infarction depends largely on the myocardial necrosis and its sequelæ. Coronary artery disease is the usual initiating factor in obstructing the blood flow to a portion of the myocardium, but once heart muscle necrosis has developed the damage to the myocardium affects the course of the disease, regardless of whether or not there is progression of coronary arteriosclerosis.

In physiologic terms, the immediate effect of acute myocardial infarction is failure of the left ventricle, the muscle of which almost always is the site of the myomalacia.[1,4,6,8] It is, however, clear to all observers that progressive cardiac failure is not apparent clinically in all cases, not even in all fatal ones. The frequency of other secondary factors causing death indicates that the heart is not necessarily damaged beyond repair in those who die from myocardial infarction. The purpose of this study is to investigate the immediate sequelæ of myocardial infarction and their influence upon the mortality from it, in patients who were observed clinically and examined postmortem, with a special effort to separate cases in which death was due to irreparable cardiac damage from those in which the cause of death was a secondary complication.

Material and Methods. The study is based on 130 consecutive cases of recent infarction of the myocardium found on gross examination in the routine autopsy material of the Department of Pathology during the 8 year period of 1937 to 1944. Doubtful cases were eliminated, and so were cases in which clinical records were inadequate for the study. No special methods of visualization of the coronary tree postmortem were used, but the coronary arteries were carefully examined and the myocardium searched, and both were studied microscopically. Clinical records were examined and particular attention was paid to the course of illness, circumstances preceding death and the mode of death.

Special care was exercised in evaluation of the patient's condition before the development of myocardial infarction, in order to separate patients who already were ill at that time. The decision as to what constitutes the immediate cause of death was reached in each case after a most careful consideration of clinical data and the autopsy findings. In cases with multiple complications one factor was selected which was thought to have had a decisive effect on the course of the disease.

In addition to the course and cause of death, pathologic evidence of damage to the heart was studied, particularly the size of the infarction, the presence of myocardial scars and of cardiac hypertrophy. Infarcts were classified according to the size as "large" and "small," and only definite myocardial scars were accepted as evidence of previous infarction, usually with a corresponding old coronary occlusion. Hearts were classified as hypertrophied if the weight exceeded 500 gm.

Findings. General Considerations. Gross pathologic descriptions of the 130 cases showed that the recent infarcts of the myocardium were diagnosed as massive in 36 cases, while in the remaining 94 cases their sizes varied from 1 to 8 cm. in diameter. Infarcts were caused by coronary arteriosclerosis in 126 cases, by coronary embolism in 3, and by periarteritis nodosa in 1. In the arteriosclerotic group, coronary thrombosis was demonstrated in 102 cases, and occurred in 1 branch in 82, and in 2 branches in 20 cases. Coronary arteriosclerosis of the branches supplying the non-infarcted myocardium was described as severe in 65 cases, moderate in 35 and mild in 26 cases. Mural thrombosis was found in 78 cases (60%).

A review of the clinical data revealed that the patients fell into 2 main categories: those in whom myocardial infarction developed as a complication of a preexisting serious illness, and those in whom infarction was in the clinical sense a primary illness. Thirty-five patients fell into the former category; 22 of them suffered from cardiac failure prior to the development of myocardial infarction and 13 suffered from non-cardiac conditions such as periarteritis nodosa, septicemia, uremia, diabetic acidosis, lobar pneumonia, cancer, lung abscess, empyema, or had myocardial infarction after a major surgical operation. In these patients the pathologic findings in the coronary arteries and the myocardium were comparable to the remainder of the series, yet, from the clinical standpoint they were thought to be unsuitable for the study of the effect of myocardial infarction upon the circulation. In patients who were seriously ill before the development of the infarction even slight damage to the myocardium may become the immediate cause of death, and myocardial infarction is a mere terminal event, comparable to bronchopneumonia. It was decided, therefore, to eliminate from the clinical-pathologic correlation these 35 cases and limit the material to the 95 cases of "primary" myocardial infarction; that is, patients who prior to the infarction had little limitation of activities, belonging to the functional Classes I and II (classification of the American Heart Association).

"Primary" Myocardial Infarction. The 95 cases of "primary" myocardial infarction were divided in 4 groups, according to the cause of death and clinical course. Group 1 included those who developed progressive circulatory failure, either congestive failure or shock, and who at autopsy did not show any important complications. There were 28 patients in this group. Group 2 consisted of 24 patients who died suddenly, but showed at necropsy no immediate cause of death other than the infarction, suggesting that death was in them due to a fatal arrhythmia. In 12 patients of this group some observations as to the mode of death were available, the remainder were found dead, or died without warning. Six patients died during various activities (walking, trying to get out of bed, straining on the bed-pan, etc.). One patient developed symptoms suggesting acute pulmonary edema and died before treatment could be started; 4 patients had attacks of anginal pain immediately preceding sudden death; 3 had convulsions. In this group at least 24 hours elapsed between the onset of the infarction and the sudden death.

Group 3 included 32 patients who died as a result of complications demonstrable at autopsy. In all patients included in this group the clinical course, mode of death and autopsy findings suggested that the complications turned the tide of a case from a possible recovery, or at least accelerated death. The following complications were found: rupture of the infarcted left ventricle was present in 8 cases (in 7 of them into the pericardium and in the eighth through the interventricular septum into the right ventricle), embolic phenomena were found in 15 cases, including cerebral embolism in 6, massive pulmonary embolism in 5, embolism to extremities in 3, and mesenteric embolism

TABLE 1.—RELATIONSHIP BETWEEN THE IMMEDIATE CAUSES OF DEATH AND THE VARIOUS TYPES OF CARDIAC DAMAGE FOUND AT AUTOPSY IN PRIMARY MYOCARDIAL INFARCTION

(Group 1: Progressive Circulatory Failure. Group 2: Sudden Death. Group 3: Death Due to Complications. Group 4: Other Causes of Death)

	Group 1	Group 2	Group 3	Group 4
Massive myocardial infarction	10	7	15	2
Old and recent infarction	8	7	2	4
Myocardial infarction and cardiac hypertrophy	6	3	7	3
Other cases of myocardial infarction	4	7	8	2
Total	28 (30%)	24 (25%)	32 (34%)	11 (11%)

TABLE 2.—RELATIONSHIP BETWEEN THE CONDITION OF PATIENTS WITH PRIMARY MYOCARDIAL INFARCTION AND VARIOUS TYPES OF CARDIAC DAMAGE FOUND AT AUTOPSY

	Patients in serious condition	Patients in good condition
Massive myocardial infarction	17	17
Old and recent infarction	12	9
Myocardial infarction and cardiac hypertrophy	8	11
Other causes of myocardial infarction	12	9
Total	49	46

TABLE 3.—DEGREE OF CORONARY ARTERIOSCLEROSIS IN VARIOUS CLINICAL GROUPS OF PRIMARY MYOCARDIAL INFARCTION*

Coronary Arteriosclerosis	Group 1	Group 2	Group 3	Group 4	Total
Mild	7	5	9	2	23
Moderate	6	6	13	1	26
Severe	15	13	10	8	46

* See Table 1.

TABLE 4.—TIME INTERVAL BETWEEN THE ONSET AND DEATH FROM MYOCARDIAL INFARCTION AND ITS RELATIONSHIP TO THE CAUSE OF DEATH

No. of days between initial attack and death	Group 1	Group 2	Group 3	Group 4	Total
1– 3	8	7	2	1	18
4– 7	7	10	10	1	28
8–10	4	2	3	2	11
11–14	7	1	3	3	14
15–21	1	3	9	2	15
22–30	..	1	5	..	6
Over 30	1	..	..	2	3

in 1. Other complications, not directly connected with the infarction were: lobar pneumonia (appearing after the infarction) in 2, empyema, diabetic acidosis, uremia, gastro-intestinal hemorrhage, unexplained ileus in 1 each. Two patients died following a surgical operation for an intercurrent condition. In 20 of the 32 cases in this group the patients were progressing satisfactorily up to the time of development of the complication, while in 12 they were in serious condition and in them complications presumably only accelerated an inevitable fatal outcome. It is of interest to note that 4 of the 5 patients with massive pulmonary embolism occurred in seriously ill patients.

Group 4 consists of miscellaneous cases, which did not fit into any of the first 3 groups. Five patients died of recurrent coronary occlusion while in the hospital for the treatment of myocardial infarction: 2 of them during the 1st and 3 in the 2nd week after the first attack. Four patients had a prolonged course with repeated remissions and exacerbations, for which no explanation was apparent. Two patients died under circumstances suggesting digitalis toxicity.

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TABLE 5.—RELATIONSHIP BETWEEN AGE AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

Age (yrs.)	Group 1	Group 2	Group 3	Group 4	Tota
Below 50	5	7	4	1	17
51–70	17	14	20	8	59
Over 70	6	3	8	2	19

TABLE 6.—RELATIONSHIP BETWEEN SHOCK AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

	Group 1	Group 2	Group 3	Group 4	Total
Patients in severe shock	5	..	2	..	7
Patients in mild shock	9	1	1	2	13
Totals:					
Patients in shock	14	1	3	2	20
Patients without shock	14	23	29	9	75

TABLE 7.—RELATIONSHIP BETWEEN LEFT VENTRICULAR FAILURE AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

	Group 1	Group 2	Group 3	Group 4	Total
Patients with severe left ventricular failure	6	1	3	..	10
Patients with mild left ventricular failure	17	11	19	8	55
Totals:					
Patients with left ventricular failure	23	13	22	8	65
Patients without left ventricular failure	5	12	10	3	30

TABLE 8.—RELATIONSHIP BETWEEN RIGHT VENTRICULAR FAILURE AND CAUSE OF DEATH IN PRIMARY MYOCARDIAL INFARCTION

	Group 1	Group 2	Group 3	Group 4	Total
Right ventricular failure	3	1	11	2	17
% of total number of patients in the group	10%	4%	34%	18%	18%

myocardial damage as recorded at autopsy and the immediate cause of death is presented in Table 1. Table 2 shows these same pathologic data correlated with the patient's condition, regardless of the cause of death. In this table the first column represents roughly patients whose chances of recovery from acute myocardial infarction appeared slight, and the second column those who had a good prospect for survival of the attack. The comparable incidence of the various pathologic findings believed to show the extent of myocardial damage in the 2 groups indicates a lack of correlation between the seriousness of the clinical course and the extent of myocardial damage.

Table 3 shows the degree of coronary arteriosclerosis with particular reference to the non-occluded vessels in the 4 clinical groups. There is a somewhat lower incidence of severe arteriosclerosis of the coronary arteries in patients who died of secondary complications.

Table 4 shows the time of death in relation to the cause of death. It shows that the time between the development of myocardial infarction and death was shorter in patients who died of circulatory failure and of fatal arrhythmia than in those who developed secondary complications. The time of death from the important complications was as follows: rupture of the heart occurred within the 1st week in 4 cases, in the 2nd week in 2, and in the 3rd week in 2. Death from embolic phenomena occurred in 5 cases in the 1st week, in 5 in the 2nd week, and in 4 in the 3rd week.

Table 5 presents the relationship between the age of the patients and the causes of death. There was a slightly higher incidence of fatal arrhythmias in younger patients; otherwise there were no striking differences in the mode of death in various age groups.

The remaining 3 tables present the incidence of various forms of circulatory failure in the 4 groups of patients. Shock (Table 6) was observed in 20 cases (21%), 14 of which occurred in Group 1, accounting for half of this group. All patients

with shock, with 1 exception, died within the first 8 days after the initial attack.

Left ventricular failure (Table 7) was noted in 65 patients (68%) and showed highest incidence in Group 1, both in frequency and severity.

Right ventricular failure (Table 8) was recorded in 17 cases (18%). There were fewer cases of right ventricular failure in Group 1, and it appeared most frequently in patients who died from secondary complications (11 cases). It was noted that in 7 of these 11 cases pulmonary complications were present, namely infarctions in 5 and pneumonia in 2.

Discussion. Patients with fatal myocardial infarction can be divided roughly into 3 types: (1) those who die within minutes or hours after the onset of coronary occlusion; (2) those who survive the initial attack, but fail to develop adequate circulatory adjustment; (3) those who show effective compensatory measures but die from secondary causes. Only the last 2 types of patients were studied here: patients with immediately fatal coronary occlusion do not live long enough to reach the hospital, and therefore were not encountered in this material. Of the 95 patients with "primary" myocardial infarction, 49 showed clinical evidence of circulatory failure; 19 died in shock, 14 in severe congestive failure without complications, and 16 had cardiac failure but died of intercurrent complications.

These 30 patients who were in severe cardiac failure and possibly the 19 patients in shock constitute cases in which the myocardium was apparently damaged beyond repair. It is shown that the incidence of massive infarcts, of old myocardial scars, and of cardiac hypertrophy in these patients is the same as in fully compensated cases. This suggests that there is no correlation between the extent of gross damage to the heart muscle and the functional capacity of the myocardium. It would perhaps be unjustified to accept unequivocally on the basis of relatively small series of cases a far-reaching conclusion, that the degree of myocardial damage does not influence the course of myocardial infarction. It is safer to interpret these findings as a mere illustration of the fact that under favorable conditions patients may develop very large infarcts, or infarcts in hearts previously damaged by heart disease, and yet show enough compensatory measures in the circulatory system to render them free from clinical signs of circulatory failure.

It appears then that the most crucial period of time in an attack of coronary occlusion is the first few moments after the onset. In most severe cases patients may not even live long enough to develop recognizable myocardial necrosis. Those patients who survive the critical first few hours apparently have effective compensatory factors working in their favor. At this stage the various secondary complications of myocardial infarction become more menacing to the patients than the derangement of the circulation.

Of the various types of circulatory insufficiency, left ventricular failure is the commonest, but the least serious of all sequelæ of myocardial infarction. In this report only fully developed left ventricular failure was recorded, but it has previously been demonstrated that latent, or mild left ventricular failure can be shown in almost every case of myocardial infarction.[5]

In contrast, right ventricular insufficiency occurs infrequently in the course of myocardial infarction, but is very serious, almost invariably fatal. It is shown that right-sided cardiac insufficiency is rare in patients who run the course of progressive circulatory failure, and occurs more often in association with pulmonary infarction or infection. It is likely that the changes in the pulmonary circulation due to these complications contribute to the overloading of the right heart. If confirmed, this relationship may be of some diagnostic value by directing attention to the possibility of pulmonary complications in cases where right ventricular failure develops prominently

in the course of myocardial infarction.

Persistent shock was present in 20% of patients and was in all of them the main or contributory immediate cause of death. The present-day inadequate knowledge of the pathogenesis of shock in myocardial infarction does not permit a definite statement, as to whether shock is entirely due to myocardial insufficiency, or in part, to peripheral circulatory failure. It is therefore not known whether it should be considered as evidence of irreversible damage to the myocardium, or a complicating factor, which, perhaps, could be favorably influenced by treatment.

Sudden death responsible for 25% of fatalities in this series is the most serious consequence of myocardial infarction. The mechanism of death in such cases is usually attributed to ventricular fibrillation, although only in the rarest cases is actual proof of this arrhythmia available. Indirect evidence is based on animal experiments[9] and on the high incidence of milder forms of arrhythmia preceding sudden death in patients with myocardial infarction. This has not been confirmed in the present series. It should also be pointed out that Weiss[7] emphasized the importance of other mechanisms of sudden death, related to overactive cardio-inhibitory reflexes. The few observations as to events immediately preceding sudden death in this series suggests that the mechanism may be different in various cases. It is also noteworthy that sudden death was in a number of patients precipitated by activity.

The importance of thrombo-embolic phenomena[2,3] as a fatal complication of myocardial infarction is fully confirmed in this series: 21% of patients died as a result of them, and 60% of cases had mural thrombi in the endocardium.

Finally, cardiac rupture is a small but definite hazard of acute myocardial infarction. The incidence of cardiac perforation in this series is comparable to that of other investigations.

The most important point brought out in this report is the fact that at least 50% of the patients who died during the acute stage of myocardial infarction had evidence of effective compensatory measures in the circulation and died because of secondary complications. This figure represents the most conservative estimate, for all patients in persistent shock and severe cardiac failure were assumed as representing irreversible cardiac damage, without consideration of the possibility that different therapy might have prevented a fatal outcome in some of them. It appears, then, that from the standpoint of pathologic changes and functional capacity of the myocardium, death is preventable in a large proportion of patients who survive the initial attack of pain of myocardial infarction. All patients in this series underwent standard treatment for myocardial infarction, and it is obvious that more effective means of prevention of secondary complications are needed if the mortality from myocardial infarction is ever to reach the irreducible minimum. The recent introduction of anticoagulants in the treatment of myocardial infarction[10] is a step in the right direction, but sequelæ of myocardial infarction other than thrombo-embolic phenomena are in need of investigation from the standpoint of prevention and treatment.

Summary and Conclusions. 1. A series of 130 unselected cases of recent myocardial infarction found at autopsy was examined. In 35 patients myocardial infarction was a terminal event in otherwise seriously ill patients and was regarded as of little clinical interest. The remaining 95 patients were apparently well prior to the onset of the myocardial infarction and were subjected to detailed analysis as "primary" myocardial infarction.

2. The immediate cause of death in this group of 95 cases was: progressive circulatory failure, with or without shock, in 28 cases; sudden death due to arrhythmia in 24 cases; embolic phenomena in 15 cardiac rupture in 8 cases; secondary coronary thrombosis in 5 cases. In the

remaining 15 cases death was due to incidental complications not related to myocardial infarction.

3. No significant correlation was found between the age of the patients, the degree of the coronary arteriosclerosis, the size of the infarction and the presence of myocardial scars and of cardiac hypertrophy on one hand, and the course, the duration of illness, and the frequency of complications on the other hand. This is interpreted as indicating the adequacy of circulatory adjustment even in cases with extensive damage to the heart.

4. The prognosis of acute myocardial infarction is unpredictable because the importance of cardiac insufficiency—the direct consequence of the damage to the myocardium—is outweighed by secondary complications. The immediate mortality is twice, or perhaps 3 times greater than the estimated number of cases with irreparable cardiac damage. The important sequelæ of myocardial infarction, which can be considered potentially preventable causes of death, are: serious arrhythmia, thrombo-embolic phenomena and shock.

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DIGITOXIN POISONING

REPORT OF 30 CASES

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Modern digitalis is a very potent drug. Like its predecessors, since the time of Withering, it has well known symptoms and signs of overdosage, intoxication, or poisoning. Using ordinary doses and with ordinary care, the physician rarely has to contend with the problem of digitalis poisoning. Therefore, when he turns to and uses the most potent of all *Digitalis purpurea* glucosides, digitoxin, in the recommended dosage, and despite care he frequently encounters the symptoms and signs (mainly) of digitalis overdosage, it is a problem that requires serious consideration.

During the period from January 1, 1947, to January 30, 1948, I had the unusual experience of seeing 30 patients with digitoxin poisoning. None of the patients had received digitalis in any form previous to the administration of the oral digitoxin in the recommended dosage. All of the physicians who treated these patients stated that the advised method and dosage for giving this digitalis glucoside were used, and that the alarming signs appeared early, from the 2nd to the 10th day, rather than late. Electrocardiograms were available in all instances, previous to, during, and after all the toxic manifestations had completely disappeared.

Serious toxic manifestations seem to have been more frequently observed from the use of the digitalis glucosides than from the whole-leaf preparations.[7] Since all my own work has been with the whole-leaf digitalis preparations[4] I may seem to be prejudiced in their favor. However, it seems clear that most of the difficulties encountered due to digitalis therapy result from the use of the isolated glucosides. The incidence of digitalis poisoning has risen in direct relation to the increased use of these glucosides.[7]

Over a period of 15 years, the last 8 associated with a large medical service at the Cook County Hospital (the Ward 61 service of Dr. Harry J. Isaacs), the writer has encountered digitalis poisoning infrequently. If one such case was seen a year, it was considered a "find" for teaching purposes. Most often it was present in a patient with long-standing decompensated rheumatic heart disease: mitral stenosis, insufficiency, and auricular fibrillation, and who would show a bigeminy with long, continued digitalis therapy. Considering the large number of cardiac patients seen and the length of time treated, the margin of safety with the whole-leaf digitalis preparations must be very great to account for the infrequency of symptoms and signs of overdosage. Until late in 1946 the common symptoms and signs of digitalis overdosage which I saw were anorexia, nausea and vomiting, occasionally with, but most often without, bigeminy, or a marked sinus bradycardia without symptoms. I had yet to see auricular fibrillation, auriculoventricular block, partial heartblock, sinus arrest, and paroxysmal ventricular

tachycardia as manifestations of digitalis poisoning. Late in 1946 and early in 1947, when many switched to the isolated digitalis glucoside preparations, cases of digitoxin poisoning began to appear.

Age, Sex and Color. A total of 30 such patients have been seen in 13 months. Their clinical data are the subject of this report. There were 17 (56%) females and 13 (44%) males, all white, whose ages varied from 21 to 72 years. The average age was 55 years. All were educated, intelligent individuals, with whom there had been no difficulty in either understanding the instructions or in the taking of the prescribed digitoxin preparations. In the series of 44 cases reported by Herrmann *et al.*[7] 25 were Negro patients, so that the authors felt that this might account for failure to understand or observe directions.

Types of Heart Disease. The types of heart disease associated with the congestive heart failure, for which the digitoxin had been given, were not significant. There were 7 with rheumatic heart disease, 7 hypertensives, 7 hypertensive-coronary cases and 1 with no heart disease. The hypertensives, either alone or in combination with arteriosclerotic (coronary) heart disease, were most common, as has been shown previously.[5]

Symptoms and Signs. Those noted in the 30 patients were mainly disorders of the cardiac mechanism, as 20 (66.6%) had no symptoms of digitoxin poisoning. The other 10 complained of anorexia, nausea, vomiting, weakness and fatigue, symptoms which had not been present previous to the digitoxin administration. No instances of diarrhea, yellow vision, or scotoma were seen. All the patients had regular rhythm at the time congestive failure occurred and when the administration of digitoxin was started. In the 44 cases reported by Herrmann and his associates,[7] the most common disorder of cardiac action was paroxysmal tachycardia with auriculoventricular block (20 cases). Among my 30 cases, the 2 chief findings were premature contractions and auricular fibrillation (Table 1). Bigeminy,[8] the clinical sign most often associated with overdigitalization, was noted in 6 (20%) of the 30 patients. S-T and T wave depression, the electrocardiographic sign most frequently seen with digitalis overdosage, was found in 19 cases, but this was the sole graphic abnormality in only 6 of the 19.

TABLE 1.
Electrocardiographic Signs in 30 Cases of Digitoxin Poisoning

Premature Contractions	11
Irregular	5
Bigeminy	6
Auricular Fibrillation	10
Auriculoventricular Block	5
S-T and T depressed	19
Alone	6
Sinus Bradycardia	4
Partial Heart-Block (P-R prolonged beyond 0.24 sec.)	4
Sinus Arrest (Dropped Beats)	2
Paroxysmal Ventricular Tachycardia	1

Only 2 deaths occurred among the 30 patients, 1 due to paroxysmal ventricular tachycardia and the other with auricular fibrillation and bigeminy. The low mortality was due to the awareness of the physicians treating these patients, but some of the doctors were greatly surprised, and chagrined, that such serious cardiac disorders oc-

curred without symptoms on the usually advised dosage of the digitoxin preparations.

Discussion. Although this report presents only 30 instances of digitoxin poisoning, it may serve to emphasize certain points. All of the patients were treated by the so-called latest development in digitalis therapy (yet digitoxin was first described as long ago as in 1869 by Nativelle).[9] The potency of digitoxin orally administered is approximately 1000 times that of U.S.P. digitalis leaf; 0.1 mg. digitoxin is equivalent to 0.1 gm. (gr. iss) whole-leaf digitalis and to 1 U.S.P. XII Digitalis Unit. Warnings were issued[6,2,4c] on U.S.P. XI Digitalis, which became U.S.P. XII in most instances, that the potency of digitalis was increased clinically about 50%. Many pharmaceutical manufacturers then advised a maintenance dose of whole-leaf digitalis of about gr. ¾. Now when these same pharmaceutical houses offer and promote very vigorously a 0.1 mg. tablet of digitoxin, considered as equivalent to 1 U.S.P. XII Digitalis Unit (which in turn ranges anywhere from gr. ss to gr. iss depending on the source, purity, and standardization of each whole-leaf preparation) the confusion becomes greater than ever. Even by adhering to all the directions and instructions issued with the digitoxin preparations, one is still not able to avoid intoxication and poisoning.

Digitoxin also has a peculiar action on the sinus rate. Braun and Wosika,[3] quoting Oettel, emphasized the so-called "paradoxical action" of the digitalis glucosides (an increase in the sinus rate and the appearance of ectopic beats). Most recently, Stone[10] reported a case of auricular tachycardia and auriculo-ventricular dissociation following 1.2 mg. of digitoxin (orally) in one dose, a combination which I have not encountered to date. In his patient, a man weighing 125 pounds, 1.2 mg. of digitoxin was considered excessive as the initial oral digitalizing dose. When part of the 1.2 mg. was eliminated the auricular tachycardia and A-V dissociation disappeared, but there was still evidence of toxicity in the prolongation of the P-R interval to 0.28 sec. Because of the high percentage of toxicity in their cases, Batterman and De Graff[1] recommended that digitoxin be made available in 0.05 mg. tablets. Since the recommended oral dose is 1.2 to 1.5 mg. at intervals of 4 to 6 hours, followed by a daily maintenance dose of 0.1 to 0.2 mg., their excellent suggestion would make possible the halving of the dosage.

From such experience it would seem that considerable caution needs to be used in the treatment of patients with congestive heart failure with the digitoxin preparations. Purified glucosides will not result in a more efficient or safer digitalization.[1] It might be safest to use a good whole-leaf preparation of *Digitalis purpurea* or *lanata*, since it has been shown to be the drug of choice for routine use.[11] It may be old-fashioned, but it certainly has a much greater factor of safety. At least the warning symptoms and signs of whole-leaf digitalis overdosage, infrequently as they occur, are easily recognized clinically.

Whenever digitoxin is used in the treatment of congestive heart failure, the appearance of signs of cardiac disorder must be watched for carefully, not only clinically but with the electrocardiograph, and such appearance should call for the immediate discontinuance of the drug.

Summary. 1. In 13 months digitoxin poisoning was seen in 30 patients who had received the regularly prescribed doses of this isolated digitalis glucoside.

2. The age and sex of the patient or the type of underlying heart disease had no relation to the occurrence of the digitoxin poisoning.

3. Symptoms, such as are known to be due to digitalis overdosage, occurred infrequently in these patients.

4. Signs of disorders of the cardiac mechanism, especially the more serious conduction disturbances, were the earliest and most frequent clinical and electrocardiographic manifestations in these cases of digitoxin poisoning.

5. Considerable caution should be exercised in the administration of the digitoxin preparations in the regularly advised dosage and form to any patient suffering with congestive heart failure, because the action may be rapidly intoxicating to the cardiac musculature and its conduction system.

6. The factor of safety for this particular *Digitalis purpurea* glucoside seems to be extremely narrow.

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MULTIPLE MYELOMA
A REPORT OF EXPERIENCE WITH STILBAMIDINE* †

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Multiple myeloma is a fairly common, progressive, fatal disease. No therapy used has been curative. Treatment with X-ray has been useful, but it has been only palliative and does not always relieve the pain which is often the most disabling feature of the disease. Snapper[1,2] has recently reported that the injection of stilbamidine exerts a favorable influence on the pain in many cases of multiple myeloma. His report emphasizes that the disease is not cured; however, relief from pain has persisted for many months.

Snapper and his associates[2,3,4,5] also observed that basophilic cytoplasmic precipitates appear in myeloma cells following treatment with stilbamidine. This observation is of great interest, and it may be one of great value in the study of this disease as well as others in which protein metabolism has been disturbed. Histochemical studies demonstrated that these basophilic granules contain a conjugation product of ribose nucleic acid and stilbamidine.

Material and Methods. Four cases of multiple myeloma are presented in this report. In each case, the diagnosis was proved by sternal marrow aspiration, tissue biopsy, or postmortem examination. Three of the cases were from the hematology service of the Veterans Administration Hospital, Portland, Oregon, and one case was from the hematology service, University Hospitals and Clinics, University of Oregon Medical School, Portland, Oregon.

All of these cases were treated with stilbamidine. The procedure outlined by Snapper[2] was followed closely. For each injection, the compound was dissolved in 10 ml. of distilled water and given within a short time of its preparation, since the solution must be administered while fresh. An initial intravenous injection of 50 mg. was given, followed 2 days later by an injection of 100 mg. Subsequently, 150 mg. intravenous injections were given every other day. The patients were hospitalized for the course of treatment. Since a diet low in animal protein is an essential part of the treatment, hospital dieticians supervised the diets daily.

Reactions to stilbamidine are mild. Those which occur early are vasomotor phenomena, a fall in blood pressure, sweating, nausea, vomiting, and venous thrombosis at the site of injection. The administration of 1/150 grain of atropine sulphate hypodermically before each injection dissipated many of these reactions. Adrenalin was found to be ineffective

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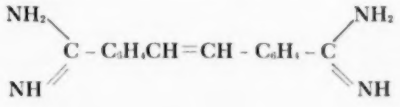
†The stilbamidine used in this study was supplied by Merck and Company, Inc., Rahway, N. J., through the courtesy of Dr. D. F. Robertson. It is a diamidine compound, 4,4-diamidinostilbene, with the formula



in combatting them. Dissociated trigeminal nerve anesthesia, a later toxic sign, was not noted in this group of cases.

Chronic renal disease is a contraindication to therapy with stilbamidine. One case (number 2) demonstrated a mild degree of renal impairment, but it was not felt to be of sufficient severity to warrant withholding the drug.

Sternal marrow aspirations were performed before the course of treatment with stilbamidine was started and following its completion. The marrow smears were stained with Wright's stain and by the modified Giemsa technique proposed by Snapper and his associates[4] for the demonstration of the basophilic cytoplasmic inclusion bodies in the myeloma cells.

Case Reports. The following 4 cases were treated with stilbamidine injections combined with a diet low in animal protein.

Case 1. W. W., a 35-year old white male, felt perfectly well until May, 1946, when he developed pain in the lower part of his back while lifting a heavy boat. He was able to do light work until the middle of June, 1946, at which time he began to notice that his legs were weak. He was admitted to the U. S. Naval Hospital, Seattle, Washington, in July, 1946, where radiograms of the spine revealed multiple bony involvement of an osteolytic character and a pathologic fracture of the 8th dorsal vertebra. He received a short course of radiation therapy and was then transferred to the Veterans Hospital, Portland, Oregon, on August 28, 1946. At this time, he complained of increasing weakness, more severe pain radiating from the back anteriorly, and pain on movement of his hips.

Examination on admission revealed a pale individual who appeared to be in a great deal of pain. There was tenderness over the lower dorsal and lumbar spine. There was no evidence of involvement of the spinal cord or of the peripheral nervous system.

His red blood count was 2.9 million and his hemoglobin 55%. The total white blood count was 3,600, with a normal differential cell count. The sedimentation rate was 55 mm. per hour (Wintrobe). The serum calcium was 15 mg. per 100 ml., phosphorus 2.7, acid phosphatase 6.2, and alkaline phosphatase 20.2. The serum total protein level was 6.5 gm. per 100 ml., with 4.8 gm. of albumin, 1.7 gm. of globulin, and an A/G ratio of 2.8 to 1. The urine did not contain Bence-Jones protein. Sternal marrow aspiration revealed 78% plasma cells, 14% staff cells, 7% neutrophils, 3% lymphocytes, and 4% nucleated red cells.

Radiograms of the spine revealed a multiple bone involvement with compression collapse of the 7th and 8th dorsal vertebrae, and all the lumbar vertebrae. There was also widespread involvement of the skull, the scapulae, the humeri, and the femurs.

He received a short course of urethane during October and November, 1946, but it was discontinued because of his persistent vomiting. On May 3, 1947, a course of stilbamidine was started. He was given a total of 30 intravenous injections on alternate days up to a final dosage of 4.5 gm.

His hospital course was progressively downhill. His blood count dropped continuously despite repeated transfusions of whole blood, and his final red blood cell count was 1.2 million and his hemoglobin 27%. His pain became more severe. On July 14, 1947, he lapsed rather abruptly into coma. He showed athetoid movements, but there were no localizing signs. He died 2 days later.

Postmortem examination confirmed the widespread bony involvement demonstrated by X-ray. In many areas there was complete destruction of osseus structures by plasma cell tumors. There was no evidence of regression of the process noted at necropsy. The myeloma cells contained basophilic cytoplasmic granules.

Case 2. R. T., a 45-year old colored female, felt perfectly well until September, 1946, when she developed pain in her left arm while picking beans. The pain was progressive, worse at night, and made it difficult for her to grip objects tightly in her left hand. She also complained of numbness of the left arm. She was examined at the University of Oregon Medical School Outpatient Clinic on September 13, 1946, and admitted to Mult-

nomah County Hospital. A neurologic examination revealed no sensory or motor changes. A lumbar puncture several days later revealed normal cerobrospinal fluid and dynamics. Radiograms of the wrist and hand showed no abnormalities. She was discharged from the hospital with the diagnosis of arthritis. While being followed in the Outpatient Clinic, she developed a severe anemia and was readmitted to the Multnomah County Hospital for several days for a transfusion of whole blood. She did not improve with therapy designed to combat her "arthritis" and anemia. She developed increasingly severe pain in the right shoulder, right hip, and right knee, and was readmitted to the Multnomah County Hospital on February 7, 1947.

On admission to the hospital, she appeared to suffer a great deal of pain with movement. Her mucos membranes were pale, and she was unable to move her right hand. Her red blood cell count was 3.0 million and hemoglobin 66%. The total white blood cell count was 6,200, with a normal differential cell count. The sedimentation rate reached 77 mm. per hour. The serum calcium was 15 mg. per 100 ml., serum phosphorus 5, and acid phosphatase 10.2. The serum total protein level was 6.9 gm. per 100 ml., with 4.8 gm. of albumin, 2.1 gm. of globulin, and an A/G ratio of 2.3 to 1. The Congo red test showed disappearance of 39% of the dye in 1 hour. The urine contained Bence-Jones protein. The specific gravity of the urine varied between 1.007 and 1.014; the urine was otherwise normal. The blood urea nitrogen was 28 to 48 mg. per 100 ml. Sternal marrow aspiration revealed only 3% plasma cells. Sternal biopsy confirmed the diagnosis of multiple myeloma. Radiograms of the right shoulder, right arm, skull, and pelvis revealed marked osteolytic involvement with typical punched out areas.

A course of stilbamidine was started on February 26, 1947. She reacted rather severely to the compound, and it was frequently necessary to space her doses farther than 2 days apart. However, she received a total of 13 intravenous injections, totaling 1.8 gm., over a period of 6 weeks, ending on April 11, 1947. After the 3rd injection, she noticed a temporary cessation of her discomfort, but the pain soon returned and became more severe.

While she was receiving the stilbamidine, she developed a lesion on her tongue which was thought to be myelomatous, but a biopsy of the area revealed only focal ulceration. She became aphonic shortly afterward, and direct examination of her vocal cords showed a central type paralysis. Following this episode, her course was progressively downhill, and she expired on April 22, 1947, death apparently due to asphyxia. Autopsy was not permitted.

Case 3. J. M. L., a 28-year old white male, developed disabling pains in the lumbar region in October, 1943, and was admitted to an army hospital. After 3 months, he suddenly developed paralysis of his legs below the hips. A laminectomy was performed, and he recovered movement in the right leg but the left remained completely paralyzed. Examination of a biopsy specimen of the osseus lesion proved it to be a myeloma or plasmacytoma, presumably solitary. Urinary control remained somewhat impaired, but rectal function was good. He was a wheelchair patient in several hospitals until September, 1946, when his wheelchair tipped over. Following this, for the first time he noticed pain at the root of his neck, and numbness of the thumb which gradually spread to involve all the fingers of the left hand. He also complained of numbness of the ulnar aspect of the right hand.

Examination on admission to the Veterans Administration Hospital, Portland, Oregon, on February 27, 1947, revealed a well nourished male who suffered marked pain on any movement. There was weakness and clonus of the right leg and ankle, complete paralysis, clonus, and a positive Babinski on the left leg, and sensation was diminished over both legs. There was diminished sensation over the entire arm and the ulnar portion of the right arm, and there was a positive Hoffman's sign on the left.

His red blood cell count was 4.9 million and hemoglobin 87%. The total white

blood cell count was 8,100, with a normal differential cell count. The sedimentation rate was 37 mm. per hour (Wintrobe). The serum calcium was 9.7 mg. per 100 ml., the phosphorus 3.75 mg., and the alkaline phosphatase 16.6 mg. The serum total protein was 7.2 gm. per 100 ml., with 4.2 gm. of albumin, 3.0 gm. of globulin, and an A/G ratio of 1.4 : 1. The urine contained Bence-Jones protein. Sternal marrow aspiration revealed 4% plasma cells, 2% myeloblasts, 5% promyelocytes, 8% myelocytes, 10% metamyelocytes, 17% staff cells, 25% neutrophils, 14% lymphocytes, and 15% nucleated red cells.

Radiograms of the cervical and dorsal spine revealed extensive bone destruction, and similar areas of destruction were demonstrated in the skull, ribs, and pelvis. The multiple nature of his diseases was apparent in these films.

During April, 1947, he received a course of radiation therapy to the cervical spine. After 1500 r, he experienced slight relief of pain, and he regained considerable strength in the left arm.

On May 3, 1947, a course of stilbamidine was started. He was given a total of 30 intravenous injections, on alternate days, up to a final dosage of 4.5 gm.

He continued to have severe pain in his back, and in addition, he had severe cramping abdominal pains which were apparently due to intramural tumors of the ascending colon and to a massive myelomatous enlargement of the medial surface of the left wing of the ilium. His course was continually downward, and he expired on October 5, 1947. Autopsy was not permitted.

Case 4. K. M. E., a 61-year old white male, was in good health until May, 1945, when he was involved in an automobile accident in which several dorsal vertebrae were fractured. In June, 1946, he developed severe pain in the middle of his back which radiated to the anterior chest and lower ribs. This pain has persisted to the present time. A sternal marrow aspiration was done in October, 1946, and a diagnosis of multiple myeloma was made. He has been hospitalized most of the time since November, 1946, first at Madigan General Hospital, Tacoma, Washington, and later at the Veterans Administration Hospital, Portland, Oregon, where he is still a patient.

Examination on admission to the Veterans Administration Hospital on June 13, 1947, revealed an obese individual, quite comfortable at bedrest but complaining of great pain with movement. There was tenderness over the dorsal vertebrae and several of the ribs, and there was crepitation suggestive of rib fractures. There was diminished sensation over the radial aspect of his left hand and forearm.

His red blood cell count was 3.4 million, with 68% hemoglobin. The total white blood cell count was 6,800, with 51% lymphocytes, 44% granulocytes, and 5% eosinophils. The sedimentation rate was 63 mm. per hour (Wintrobe). The serum calcium was 12.5 gm. per 100 ml., the phosphorus 4.0, acid phosphatase 7.6, and alkaline phosphatase 28.5. The serum total protein level was 8.4 gm. per 100 ml., with 4.35 gm. of albumin, 4.05 gm. of globulin, and an A/G ratio of 1.07 to 1. The urine did not contain Bence-Jones protein. Sternal marrow aspiration revealed 37% plasma cells, 7% myeloblasts, 3% myelocytes, 4% metamyelocytes, 6% staff cells, 8% neutrophils, 24% lymphocytes, and 11% nucleated red cells.

Radiograms of the entire vertebral column, pelvis, and skull revealed a diffuse process of extreme demineralization of all the bony structures. In the pelvis, there were large circular areas of bone destruction, and throughout the entire skeletal system there was riddling of small varying-size circular punched-out areas. This was true also of the skull and all of the ribs. The vertebral bodies showed varying degrees of collapse.

On June 30, 1947, a course of stilbamidine was started, and he received a total of 30 intravenous injections, on alternate days, up to a final dosage of 4.5 gm. Bone marrow smears after treatment was completed revealed the typical basophilic cytoplasmic granules in the myeloma cells.

His pain has become progressively more severe, and he is almost completely bedridden because of it. His anemia has become more marked.

Discussion. Bone pain was the out-

standing symptom of which each of the patients complained; 2 had fairly severe pain and 2 had only mild pain. Additional patients without pain were not treated. This series of cases was otherwise unselected. In only 1 instance was pain actually relieved, and this relief was only transitory. The 3 patients who expired were not regarded as being terminal when treatment with stilbamidine was started.

Sternal marrow aspirations were done on each case following the completion of the course of treatment with the drug. Three of the cases received a total of 4.5 gm., and 1 received 1.8 gm. Basophilic cytoplasmic inclusion bodies were found in the myeloma cells of 3 of the cases. Case No. 3 did not have enough myeloma cells in his sternal marrow smear to demonstrate granules, and, as a postmortem examination was not done, the tissues were not analyzed for the presence of stilbamidine[4]. Since no aspirations were performed until after the treatment had been completed, an estimation of the amount of drug necessary to produce inclusion bodies in the myeloma cells was not made. This was studied by Snapper and his associates.

Summary and Conclusions. Four patients with multiple myeloma were treated with stilbamidine. None of them received any degree of persistent symptomatic relief, and there was no evidence that the progress of the disease had been checked in any of the patients. Three of the patients expired within a short time after their course of treatment had been completed. Basophilic cytoplasmic granules were found in the myeloma cells following treatment with stilbamidine.

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CORRELATION BETWEEN THE CHOLECYSTOGRAM AND THE SECRETIN TEST FOR GALL BLADDER FUNCTION

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Shortly after the discovery of secretin and its effects on the pancreas it was found that extracts of intestinal mucosa also had cholagogue and choleretic effects. The cholagogue action has in recent years been studied in several laboratories and, mainly through the efforts of Ivy and his co-workers (1928, 1937), has been found to be due to an active principle of the small intestine cholecystokinin) which is distinct from secretin. The choleretic action of intestinal extracts is probably due to at least 2 distinct principles (Friedman and Snape, 1945). One of these has been designated hepatocrinin; it stimulates the liver to secrete bile but is without effect on the pancreas. The other is secretin, which excites both the liver and the pancreas. Evidence that purified preparations of secretin excite the flow of liver bile as well as pancreatic juice has been offered by Mellanby (1927, Still, McBean and Ries (1931–32), Agren (1934), Friedman and Snape (1945), and others. The secretin prepared by the procedure of Friedman and Thomas (1947) has been found to have the dual effect on the liver and pancreas which other investigators have reported for secretin prepared by different procedures (Pincus, Friedman, Snape, and King, 1948).

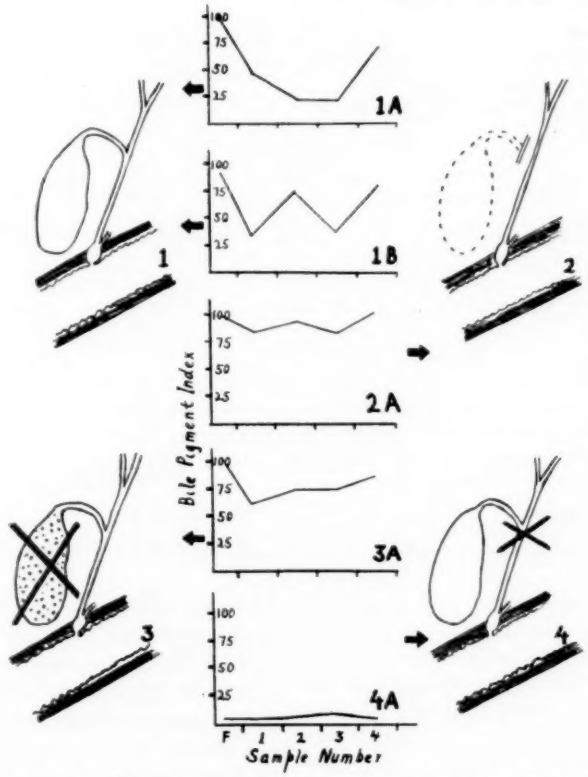
The property of secretin to stimulate the flow of liver bile as well as the flow of pancreatic juice has been utilized as a test of gall bladder function (Agren and Lagerlöf, 1937; Diamond, Siegel, and Myerson, 1940). In the normal subject the increased amount of bile secreted by the liver following secretin administration is taken up by the gall bladder where it is subjected to concentration. Following secretin injection the duodenal content thus consists mainly of pancreatic juice and occasionally some bile. The icterus index curve of the duodenal content shows only an occasional high point after the secretin injection and is generally of the configuration shown by Figs. 1A or 1B or some variant of these.

In individuals with cholecystectomy the storage space for the secretin-stimulated liver bile is absent and consequently the bile flows directly into the intestine so that all samples of duodenal content consist of pancreatic juice with a high color index (Fig. 2A). In the patient with a non-functioning gall bladder the condition is essentially similar to that in the cholecystectomy patient, in that the secretin-stimulated liver bile enters directly into the duodenum (Fig. 3A).

In the patient with obstruction of the bile ducts there is complete absence

of bile pigment from the intestinal contents (Fig. 4A). In such cases there is, of course, the obvious jaundice. In non-obstructive jaundice of hepatic origin there is usually a normal type of biliary pigment curve for the intestinal content, except when hepatic damage is severe enough to interfere with the secretory functions of the liver.

In the present study the secretin test was used on 64 patients. Except for 10 patients with cholecystectomy, each patient also had a thorough radiologic examination of the gall bladder. The correlation between the findings of the 2 tests is reported. For the purpose of this study it is necessary to emphasize that the secretin used was free from cholagogic effect as determined by the method of Snape, Friedman, and Thomas (1948).



Figs. 1A, 1B, 2A,—4A. Bile pigment indices of duodenal contents. (See text for details.)

Agren and Lagerlöf (1937), Elvin (1939), and Diamond, Siegel, and Myerson (1940) were among the first investigators to use secretin as a test of gall bladder function. They, as well as Pollard, Miller, and Brewer (1942), and Andrus, Lord, and Lake (1942) found the test to accord well with the clinical findings. In most of the patients studied cholecystographic examination was not performed.

Methods. Subjects selected for study were volunteers, ambulatory patients attending various out-patient clinics of the hospital, and patients from the medical and surgical wards. The subjects presented themselves in the Gastro-intestinal Clinic after an overnight fast. A double-lumen tube of the Lagerlöf type was passed into the intestine and exact posi-

tion of the tube checked by fluoroscopy. The gastric and duodenal contents were collected separately by continuous aspiration at a negative pressure of 30 to 50 mm. Hg. In each case a basal control period of 20 to 30 minutes duration was instituted before injection of the secretin. Secretin, prepared by the procedure of Friedman and Thomas (1948) was then given intravenously at a dosage level of 1.1 clinical units (Agren and Lagerlöf, 1936) per kilogram body weight. (In a few instances the standard dose of 80 clinical units of secretin was given without reference to body weight; this was found to be equally satisfactory). Constant aspiration of the gastric and duodenal contents was continued for the next 60 minutes, with the samples being divided into fractions collected at the end of 10, 20, 40 and 60 minutes. The bile pigment concentration in the duodenal drainage material was determined by the method of Malloy and Evelyn (1937).

Radiologic visualization of the gall bladder was performed with Priodax (beta-(4-hydroxy-3, 5-diiodophenyl)-alpha-propionic acid). This was given in dose of 3 gm. after a light fat-free evening meal. Approximately 15 hours after the ingestion of the Priodax, and while still fasting, the patient was subjected to roentgenography in the usual manner. After partaking of a fatty meal the patient was restudied roentgenographically 1 hour later to determine the amount of shrinkage of the gall bladder shadow. This served as an index of gall bladder evacuation, and added another criterion of gall bladder function.

Result. The results of the secretin test and the cholecystogram are summarized in Table 1. Classification of the patients in this table is on the basis of clinical findings and pertinent laboratory data.

Included among the 64 subjects studied were 8 patients with diseases not referrable to the digestive system and 7 patients in whom exact diagnosis was not established. In 13 of these 15 cases both the secretin test and the cholecystogram showed a functioning gall bladder. In the remaining 2 cases (Table 2: Miss A. M.; Miss H. M.) the cholecystogram was essentially normal but the secretin test (performed twice on each patient) showed the gall bladder incapable of taking up all of the liver bile.

In 10 of the patients, the gall bladder had been removed surgically at some time (3 months to 12 years) prior to our study. Cholecystograms were not taken in these patients. As might be expected, the secretin tests yielded intestinal contents of high icterus index (Fig. 2). Four of these patients were regarded as showing post-cholecystectomy symptoms, but at the time of

TABLE 1.

Results of Secretin Test and Cholecystogram in 64 Patients

Clinical Diagnoses	No. Cases	Both Tests Functioning	Both Tests Non-function	Disagreement between tests
Gastro-intestinal disease	47			
Cholecystectomy	10		10*	
Gall bladder disease	9	2	5	2
Liver Disease	2	1	1	
Pancreatitis	11	6	4	1
Ulcerative colitis	7	3	1	3
Diarrhea	4	3		1
Miscellaneous	6	6		
Non-gastro-intestinal diseases	8			
Psychoneuroses	3	3		
Miscellaneous	5	5		
Not diagnosed	7	5		2
Total Number Cases	64	34	21	9

*Only secretin tests were performed on the patients with cholecystectomy.

study neither sphincteric spasm nor bile duct obstruction was suggested by the bile pigment curve of the intestinal contents.

The diagnosis of gall bladder disease was established in 9 patients. In 5 of these patients the secretin test and the roentgenographic findings agreed with the clinical diagnosis of non-functioning gall bladder. In 2 patients both the cholecystogram and the secretin test indicated good gall bladder function. In one patient the secretin test showed a non-functioning viscus,

TABLE 2.

Summary of Data in 9 Cases with Disagreement between Secretin Test Result and Cholecystrogram.

Miss A. M.: age 32, 115 lb. Right uretral stricture and ptosis of right kidney. Normal cephalin-cholesterol flocculation. Other laboratory data negative. Cholecystogram April 2, 1947: gall bladder well visualized, and evacuates well. Secretin test Sept. 20, 1946, and March 28, 1947: gall bladder non-functioning on both occasions.

Miss H. M.: age 35; 88 lb. Low grade fever of unknown origin. Possible uretropelvic stricture. Liver function test (bromsulphalein, cephalin-cholesterol flocculation, thymol turbidity, van den Bergh) all negative. Cholecystogram Nov. 15, 1946: gall bladder well visualized. Secretin test Sept. 30, 1946, and Oct. 4, 1946: gall bladder non-functioning on both occasions.

Mrs. A. A.: age 24; 134 lb. Cholecystitis and cholelithiasis. Right upper quadrant pain of colicky nature. Marked psychic overlay. Cholecystogram Oct. 17, 1946: gall bladder poorly visualized, floating calculi. Secretin test Oct. 11, 1946: gall bladder non-functioning.

Mrs. O. H.: age 31; 105 lb. Cholecystitis and diabetes, chronic alcoholism. Acute pancreatitis, onset of symptoms Oct. 18, 1946. Cholecystogram Oct. 25, 1946: gall bladder non-functioning; repeated cholecystogram Oct. 30, 1946: gall bladder visualized, (calculi?). Secretin test Oct. 31, 1946: gall bladder non-functioning.

Mr. G. P.: age 27; 135 lb. Pancreatic fibrosis and diabetes. Nocturnal diarrhea. Laboratory: histamine-resistant achlorhydria; spinal fluid protein 216, 264, 608 mg. per 100 cc. on 3 occasions; fasting blood sugar 380 mg. per 100cc.: high fat content in stool; Wassermann negative. Cholecystogram Sept. 26, 1946: gall bladder not visualized. Secretin test Sept. 23, 1946 and April 30, 1947: functioning gall bladder on both occasions. Died October, 1947. Post-mortem findings: small firm pancreas with congestion and fibrosis, no cysts. Gall bladder normal, no stones, ducts patent.

Mr. D. McG.: age 31; 124 lb. Non-specific ulcerative colitis without marked bowel frequency. Liver function tests negative, pancreatic function normal. Other laboratory data negative. Cholecystogram June 17, 1947: gall bladder well visualized with good evacuation. Secretin test June 6, 1947: gall bladder non-functioning.

Mr. J. A.: age 18; 136 lb. Non-specific ulcerative colitis without diarrhea. Liver and pancreatic functions normal. Urine negative. Cholecystogram June 24, 1947: gall bladder well visualized and evacuates well. Secretin test June 6, 1947: gall bladder non-functioning.

Mrs. M. C.: age 42; 130 lb. Non-specific ulcerative colitis with marked tendency to constipation. Liver and pancreatic function tests negative. Cholecystogram Sept. 29, 1947: gall bladder well visualized and evacuation good. Secretin test June 23, 1947: gall bladder non-functioning.

Mrs. C. D.: age 53, 89 lb. Non-tropical sprue, osteoporosis; diarrhea with large quantites stool fat. Serum phosphorus 1.85, serum calcium 6.8 mg. per 100 cc. Small bowel deficiency pattern by X-ray. Cholecystogram Jan. 22, 1947; faint shadow suggesting impaired gall bladder concentrating power. Secretin test Jan 3, 1947: gall bladder functioning. Died Aug. 15, 1947. Post-mortem findings: acute necrosis of liver, atrophy of mucosa of stomach and ileum, pancreas normal, gall bladder large, thin, distended with bile, no bile duct obstructions.

which, although visualized roentgenologically, showed small calculi floating in the upper third (Table 2: Mrs. A. A.). In the 9th patient (Table 2: Mrs. O. H.) a cholecystogram showed the gall bladder to be non-functioning; when repeated 5 days later the gall bladder could be visualized. The secretin test led to the conclusion that the gall bladder was not functioning.

Two patients with jaundice at the time of the studies are included in the series. One patient gave a normal type of biliary pigment curve for intestinal contents by the secretin test and showed a gall bladder which could be well visualized. The patient was believed to have a mild hepatitis which abated spontaneously with disappearance of the jaundice in about ten days. The other patient was suspected of having obstructive jaundice. Both tests showed the gall bladder to be non-functioning. At operation a carcinoma of the head of the pancreas with involvement of the common duct and gall bladder was found.

Eleven of the patients at the time of our study were diagnosed as having chronic pancreatic insufficiency. In 7 cases the diagnosis was confirmed by biopsy or at operation or necropsy; in the other 4 cases the diagnosis was made on laboratory findings (including the secretin test for pancreatic function). In 5 of these patients the cholecystogram and secretin tests showed the gall bladder capable of concentration, while in 4 patients both tests agreed in showing a non-functioning gall bladder. In 1 case with diarrhea the gall bladder could not be visualized radiographically, but showed a normal type of bile pigment curve with the secretin test. The pertinent data in this patient are shown in Table 2 (Mr. G. P.).

Of 16 patients diagnosed as having gastro-intestinal disorders which did not involve primarily the biliary tract, liver or pancreas, there was disagreement between the results of the 2 tests in 3 cases (Table 2: Mr. D. M. G.; Miss J. A.; and Mrs. M. C.). These 3 patients were all among a group of 7 who had non-specific ulcerative colitis; in each the gall bladder was well visulized but the secretin test suggested a non-functioning viscus. A 4th patient showed an abnormal gall bladder by both tests, while in the remaining 3 ulcerative colitis patients the gall bladder was considered normal by both tests.

Normal gall bladder functions were shown by both tests in 2 patients with diarrhea who gave no evidence of organic lesions of the colon or of pancreatic insufficiency. In a 3rd patient, diagnosed as having non-tropical sprue, the cholecystogram showed a faint gall bladder shadow suggesting impaired function, but the secretin test suggested a functioning organ (Table 2: Mrs. C. D.).

Discussion. The cholecystographic test and the secretin test are both measures of the gall bladder's capacity to fill and concentrate hepatic bile. Interpretation of the results of each test must take into consideration the influence of certain factors, only some of which are common to both tests and some of which are not primarily dependent on the gall bladder.

In the secretin test the period of observation is usually 1 hour, while in the cholecystogram the time between ingestion of the Priodax and the roentgenologic study is between 15 and 18 hours. It is possible that in some cases a gall bladder with only a slight impairment in concentrating functions may during the 15 to 18 hours concentrate sufficient radio-opaque dye to make it visible roentgenographically, and yet not remove during the 1 hour secretin test enough liver bile to alter appreciably the duodenal bile pigment

index from that found in the cholecystectomy patient. Perhaps it may be significant that in 7 of the 9 studies in our present series which showed disagreement between the 2 tests, it was the secretin test that indicated the gall bladder to be "non-functioning."

In the patients with jaundice the recovery of colorless duodenal contents following secretin administration has been interpreted as indicating obstruction of the biliary tract and that the secretory functions of the liver are not impaired. However, it must be borne in mind that in extensive liver damage the secretion of bile may be so reduced as to give also a colorless duodenal content. As has already been pointed out, (Golden, 1941), the excretion of radio-opaque dye by the damaged liver may be sufficiently reduced likewise to make interpretation of the cholecystogram difficult.

Particularly important in the oral cholecystogram is the absorptive state of the intestine. When malabsorption is suspected, as in diarrhea of pancreatic origin, in coeliac disease, and in so-called idiopathic hypermotility of the bowel, the intravenous type of cholecystogram is suggested. Presumably, in such cases, the secretin test would be more informative than the oral cholecystogram. This is shown in cases G. P. and C. D. (Table 2): the secretin test in each was normal but the cholecystogram was not. At autopsy no evidence of gall bladder disease was found in either patient.

Because of close anatomic and physiological relationships the biliary tract and pancreas frequently are found non-functioning in the same individual. In the present series, 4 out of 11 cases with chronic pancreatitis were found to have non-functioning gall bladders while in another study of chronic pancreatic insufficiency Snape and Friedman (unpublished) concluded that the gall bladder was non-functioning in 8 out of 17 cases. The use of secretin has the advantage in that the functional states of both pancreas and gall bladder may be determined simultaneously. However, secretin as a test of gall bladder function has its limitations in that it indicates only the capacity of the gall bladder to concentrate bile: the presence of bile stones is shown only by radiologic studies. Microscopic examination of the duodenal contents following secretin administration may be helpful.

Conclusion and Summary. Cholecystographic and secretin tests of gall bladder function were performed in a series of 64 patients. In 55 patients the conclusions drawn from both tests were the same, while in 7 cases the findings from the secretin test disagreed with those from the cholecystogram. In 2 of these 7 cases the secretin test and subsequent autopsy both revealed the gall bladder to be normal, but the cholecystogram suggested a non-functioning organ. In 2 other cases the secretin test showed the gall bladder to be non-functioning: the gall bladder, while visualized, was seen to contain calculi.

The secretin test showed a high degree of correlation with the clinical diagnoses. The secretin test is not suggested as a substitute for the much simpler procedure of cholecystographic examination. However, we think it is a useful supplement to the usual procedures and recommend it when the data from the cholecystogram are difficult to interpret.

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PSEUDOMONAS SEPTICEMIA AND ENDOCARDITIS

Report of a Case

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PSEUDOMONAS AERUGINOSA (B. pyocyaneus) is frequently found on normal skin and is commonly associated with infection of the skin and the urinary tract. Rarely, this organism acquires more invasive properties, and produces widespread lesions[2,4,5]. In the case here reported an infection by pseudomonas aeruginosa led to generalized sepsis with protracted involvement of many organs, and to massive endocarditis. The rarity of this condition prompts the present case report.

Case report: G.S., a 40 year old white man, was admitted to the Service of Dr. I. S. Ravdin on 10-28-46 with complaint of severe abdominal pain. Eighteen days prior to admission he was dazed for 2–3 hours following an automobile accident. For several years he has experienced episodes of hematemesis and 3 days after the accident he had vomited a quantity of bright red blood. The following day he experienced sharp severe epigastric pain which persisted until admission. No jaundice or elevation of temperature had been present.

Physical examination revealed a blood pressure of 110/70, a rectal temperature of 101°F, a pulse of 80, and respirations of 28 per minute. The patient was well developed and well nourished. He appeared to be acutely ill. The respirations were shallow; the heart sounds were good and there were no murmurs heard. The heart was not enlarged to percussion. The abdomen was distended; peristalsis was normal. There was generalized abdominal tenderness, most marked in the epigastrium.

Laboratory data: Hemoglobin 11.6 grams %; WBC 100,800 per cu. mm. Serum amylase on admission was 400 Somogyi units per cc. Three days later it reached 1218 units per cc. Urinalyses were repeatedly within normal limits.

The symptoms persisted and the temperature ranged between 101 and 102.4 F. for the next 3 days. The clinical impression was acute pancreatitis.

Operation: On 11-2-46, four days after admission, an exploratory laparotomy was performed. The pylorus and first portion of the duodenum appeared normal. The pancreas was not swollen to palpation and there was no evidence of fat necrosis. At the root of the small bowel mesentery extending to the sacral promontory, a large mass of edematous tissue was present. Needle aspiration of this mass yielded cloudy fluid which was rich in amylase. A biopsy of the posterior peritoneal tissue showed the usual findings of inflammation. Culture from the biopsy site grew only a few diphtheroids. The retroperitoneal area was drained transabdominally and the abdomen closed.

Treatment postoperatively included repeated transfusions of whole blood, intramuscular penicillin 37,500 units every 3 hours and streptomycin 0.25 gm. every 4 hours. Penicillin and streptomycin were stopped 4 days postoperatively because of the appearance of a skin rash which subsided rapidly after the drugs were withdrawn.

The postoperative course was marked by a septic temperature which lasted until 11-13-46. There was a rather copious watery drainage through the abdominal

drainage tract which contained over 3200 units of amylase per cc. The drainage decreased gradually and the patient regained strength. He was discharged on 11-27-46 with only slight drainage persisting.

His course was uneventful until 12-29-46 when he suddenly experienced severe epigastric pain which radiated through to the back. This pain remained constant for 4 days. Following this he was asymptomatic until 1-16-47 when a similar episode recurred and again subsided in a day or two. On 2-12-47 he was suddenly stricken with severe back pain which radiated to the left loin. This continued until admission on 2-14-47.

Physical examination at this time revealed a blood pressure of 92/55, pulse of 72, and temperature of 98.6. The patient complained of considerable pain made worse by recumbency. Extreme abdominal tenderness and rigidity were present, especially in the mid-epigastrium. The lungs were normal. There was no cardiac enlargement and no murmurs were present. Heart rhythm was normal and the pulse was full and slow.

Laboratory data: Hemoglobin 13.6 grams %, WBC 18,900 per cu. mm. with 79% neutrophils. Serum amylase 275 units per cc. Urinalysis was within normal limits.

Operation: Laparotomy revealed a very much enlarged pancreas which along with the duodenum, and cystic and common ducts was involved in an inflammatory mass. A great deal of edema was present in the retroperitoneal tissues, gallbladder, and posterior gastric wall. No fat necrosis was noted. The peritoneum was split and the head and tail of the pancreas drained with Penrose drains. No stones were palpated in the gallbladder.

Treatment included intramuscular streptomycin 0.25 gm. and penicillin 100,000 units every 3 hours.

The postoperative course was uneventful, and he became afebrile 4 days after operation. Serum amylase ranged from over 400 units per cc. on 2-15-47 to 102 units on 2-28-47. A cholangiogram done on 2-21-47 showed a large common duct with no evidence of obstruction. On 2-26-47 pancreatic studies showed a dissociation of enzymes: low amylase secretion with tryptase and lipase in the normal range. No response to urecholine occurred. This was interpreted[3] as being typical of chronic pancreatitis. The patient was discharged on 3-1-47 much improved.

For about 2 months he was asymptomatic, but on 4-26-47 he was again stricken with severe abdominal pain and repeated vomiting. He was again admitted to the hospital.

Physical examination: Temperature 98.2 F., Blood pressure 122/84. There was a suggestion of scleral icterus. The heart was normal in size, and no thrills or murmurs were present. There was moderate tenderness and rigidity of the right upper abdominal quadrant. Peristalsis was decreased. No organs or masses were palpated.

Laboratory data were similar to those of the previous admission. In addition the Van den Bergh reaction was: Direct-immediate, Indirect 7.5 mg%. Serum amylase was over 500 units per cc.

The following day the jaundice rapidly deepened, the temperature rose to 104 F., and the blood pressure fell to 70/40. He vomited 300 cc. of dark brown material, and became somewhat dyspneic. A diagnosis of recurrent pancreatitis, with secondary cholangitis, was made.

Operation: After the hypotension was overcome by the use of transfusions of blood and plasma the abdomen was again explored. The gallbladder appeared acutely inflamed and the fundus appeared to be almost gangrenous. The mucous membrane bled freely after the viscus was decompressed. The duodenum was markedly edematous and the pancreas was firm but not enlarged. No other pathologic process was detected. Cholecystostomy was done. Peritoneal culture showed non-hemolytic streptococci and Pseudomonas aeruginosa. The latter organism was also grown from the gallbladder bile.

His postoperative condition was at first precarious, but after 10 days his febrile reaction gradually subsided and his jaundice decreased. Serum amylase decreased from 858 Somogyi units per cc. on his first postoperative day to normal levels

a few days later. He was discharged afebrile and without jaundice on 5-25-47 with the cholecystostomy tube in place.

He again did well until 6-3-47 when his temperature suddenly rose to 105.8 F. following a shaking chill. He had 3 subsequent chills in the next 6 days, and he was readmitted on 6-9-47. His only complaints were chills, fever and weakness.

Physical examination: Blood pressure 105/50; temperature 103.4 F.; pulse 118; respirations 34 per minute. He was slightly dyspneic. The lungs were clear and the heart appeared to be normal. There was slight epigastric tenderness and the cholecystostomy tube was draining small amounts of bile. Peristalsis was normal.

Laboratory data: Hemoglobin 8.9 gms. %; WBC 16,900 per cu. mm.; neutrophils 81%; Van den Bergh: Direct immediate, Indirect 1.1 mg. %.

Operation: The fever persisted, but his condition was certainly less acute than on any previous admission, and it was decided that a definitive operation should be done at this time of relative quiescence. On 6-13-47 the abdomen was again explored. The liver was large and soft and a liver abscess was suspected, but several needle aspirations in the liver substance yielded no pus. The pancreas was firmer than normal but not as swollen as at the last exploration. A cholecystectomy was done, and biopsy from the head of the pancreas was taken which proved to be normal pancreatic tissue. The common duct was normal in size, and no stones were palpated.

Blood culture on the first postoperative day, 6-14-47, showed Pseudomonas aeruginosa in pure culture. Sensitivity tests of the pseudomonas organisms grown from the blood were as follows: Penicillin —not sensitive to 10 units per cc., streptomycin—sensitive to 500 to 1000 units per cc.

His temperature ranged between 102 and 104.8 F. for the remainder of his course. On 6-15-47 a few petechiae were found in the palpebral conjunctivae, and slight ankle edema was noted. Intramuscular penicillin 100,000 units every three hours was started on admission. The following day intramuscular streptomycin 0.25 gm. every three hours was also given. More conjunctival petechiae appeared on 6-16-47, and a sternal marrow culture grew Pseudomonas aeruginosa. On 6-17-47 blowing systolic aortic and apical murmurs appeared, and slight cardiac enlargement was detected. It was obvious that his condition was not improving, and on the basis of the sensitivity studies on the offending organism, streptomycin was stopped. Through the courtesy of Dr. Frank Meleny a pyocyaneus phage (not autogenous) was adminstered beginning on 6-22-47. (One half cc. diluted 1:10 was given intravenously every 4 hours). Obvious signs of aortic regurgitation developed, and the course was steadily downhill. On 6-23-47 petechiae appeared over the entire body. Despite all efforts at supportive treatment including digitalis he expired on 6-24-47.

Autopsy (1 hour postmortem): The body was that of a well developed, well nourished white male weighing 71 kg., and measuring 178 cm. There was generalized edema of trunk, genitalia, and extremities. Numerous conjunctival petechiae were noted. An upper midline abdominal surgical wound was present; this showed superficial dehiscence, but in its deeper portion it was firmly adherent to the liver. About 500 cc. of blood, both fluid and clotted, was present in the peritoneal cavity.

The heart weighed 440 grams. Its surface was studded with petechiae. There was a moderate degree of left ventricular enlargement, the wall measuring 15 mm. in thickness. Engrafted upon the aortic valve were large, soft, pale, fleshy vegetations, up to 8 mm. in height, which almost covered the cusps (Fig. 1). The left leaflet showed a perforation 3 mm. in diameter. No evidence of previous aortic valvular disease was noted. The other valves appeared normal. Microscopically, the endocardium was infiltrated with various types of inflammatory cells; plasma cells predominated, but neutrophils and eosinophils were also present in small numbers. In the myocardium were scattered areas in which the muscle fibers were pale, granular, and vacuolated. In some of these areas there was a slight

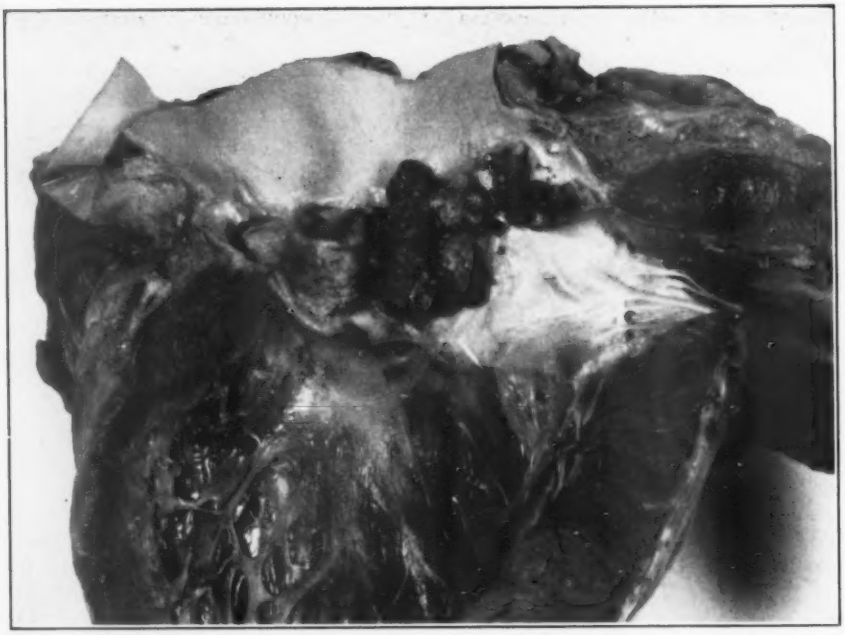

Fig. 1.—Heart: The aortic cusps are covered by pale, fleshy vegetations. There is hypertrophy of the left ventricle.

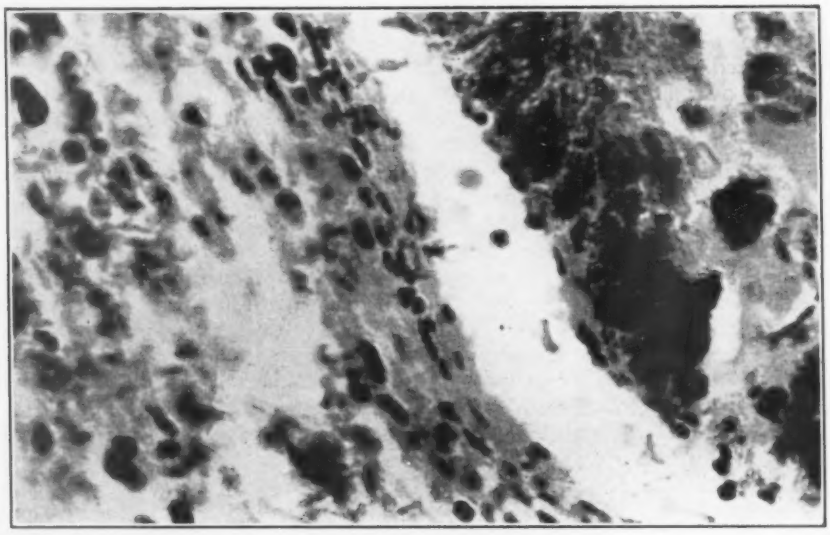

Fig. 2.—Aortic cusp: In the center of the field, and toward the right, is a massive colony of Pseudomonas aeruginosa consisting of rod-shaped bacilli extending radially. On the left is tissue reaction consisting of fibroblasts, lymphocytes and plasma cells. (Gram stain 720×).

infiltration of neutrophils, but in most there was little response of inflammatory cells. Plasma cells however were diffusely scattered through the myocardium. In the epicardium, cuffs of plasma cells extended about some of the small vessels. Section of the aortic vegetation showed a fibrin thrombus which contained large masses of gram negative bacilli (Fig. 2).

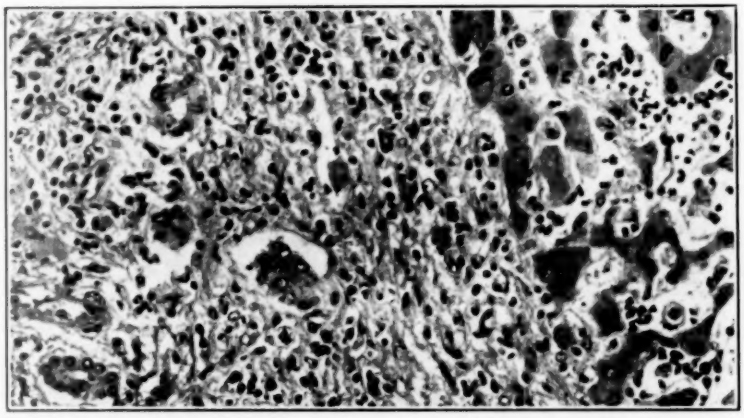

Fig. 3.—Liver: There is extensive increase in periportal fibrous tissue with marked proliferation of small bile ducts. This tissue is infiltrated with plasma cells and lymphocytes. The hepatic cords are atrophic, and the sinusoids contain numerous inflammatory cells. (H and E, 244×).

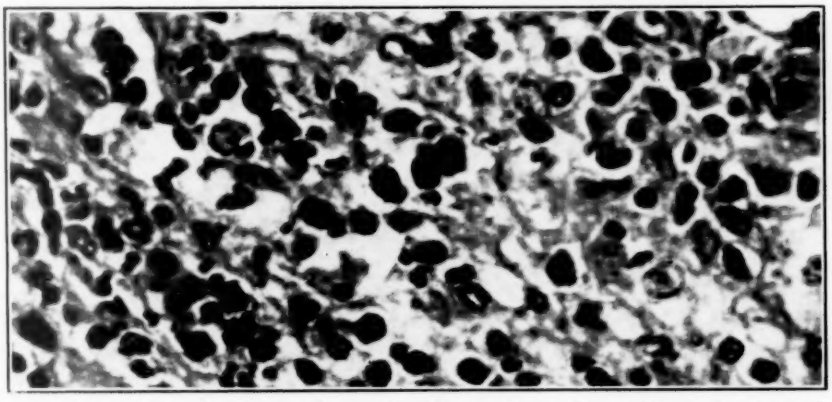

Fig. 4.—Liver: The hepatic cords are shrunken and atrophic. Filling the sinusoids are large numbers of inflammatory cells, principally plasma cells. (H and E, 450×).

The lungs were in a state of passive congestion; no other alterations were detected.

The liver weighed 4650 grams. In the dome were 3 separate abscesses, each approximately 25 mm. in diameter; they were thick-walled and contained yellow pus. Microscopically, the content of the abscesses was composed of necrotic debris, yellow-green crystals, bacilli, neutrophilic granulocytes, and foamy macrophages. The walls were fibrous with numerous macrophages and a few giant cells. The liver in general presented a considerable increase in periportal connective tissue, irregularly distributed, which was associated with a proliferation of the small bile ducts and an infiltration of plasma cells and lymphocytes (Fig. 3). The hepatic cords were shrunken and atrophic throughout, and the sinusoids were distended with inflammatory cells, principally plasma cells and neutrophils (Fig. 4).

The spleen was considerably swollen, and weighed 640 grams; there were a few small infarcts. Microscopic examination revealed numerous plasma cells in the sinusoids as the most conspicuous alteration.

The pancreas was stony hard, especially so in the region of the head. In this area white nodules of fat necrosis were noted. Microscopically the parenchyma ap-

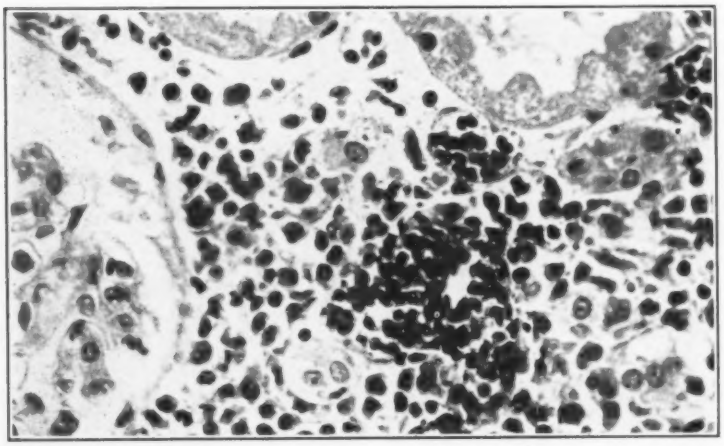

Fig. 5.—Kidney: The tubules are spread apart by dense infiltration of inflammatory cells, principally plasma cells, in the interstitial tissues. (H and E, 450×).

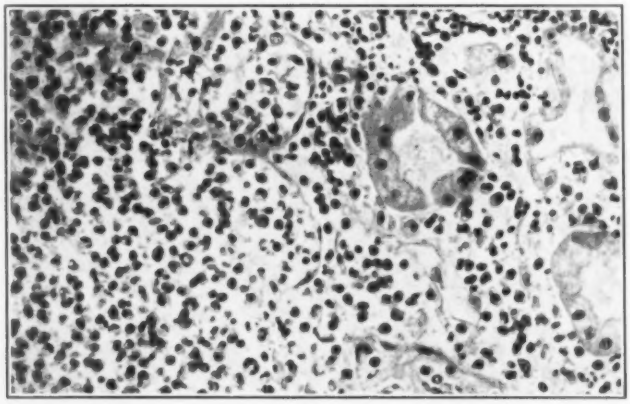

Fig. 6.—Kidney: Edge of a microscopic abscess. The inflammatory cells which are principally polymorphonuclear leukocytes extend between the tubules. (H and E, 262×).

peared normal, but the interlobular tissue was densely fibrosed and contained walled-off foci of necrosis.

The adrenals weighed 14 grams (left), and 21 grams (right). A cortical adenoma measuring 15 mm. in diameter was present in the right gland. Microscopic examination revealed slight interstitial infiltration of lymphocytes and plasma cells.

The kidneys weighed 350 grams (left), and 350 grams (right). They were large, soft, and pale, and the cortex was thickened. Microscopically, linear interstitial infiltrations of plasma cells were seen in both cortex and medulla, principally the latter. (Fig. 5). In addition there were a few recent minute abscesses in which neutrophils constituted the predominant cell type (Fig. 6). The cells of the convoluted tubules showed extensive hydropic degeneration.

In sections of lymph node and bone marrow extensive infiltration with plasma cells was noteworthy.

Postmortem cultures obtained from 2 liver abscesses, peritoneal fluid, and aortic vegetation all showed Pseudomonas aeruginosa.

Cultural Characteristics of Organism. On smear the causative organism proved to be a medium-sized Gram-

negative rod, which showed active motility in wet preparations. On agar, rough, spreading colonies were formed, which had a grape-like odor, and which were surrounded by large zones containing yellow-green pigment which was fluorescent under ultra-violet light. In broth a slight pellicle was formed, and the medium was colored green. The pigment was chloroform soluble. None of the laboratory sugars was fermented; gelatin was liquified slowly, and there was questionable production of hydrogen sulfide. Growth occurred in Koser's medium; there was questionable acidification of litmus milk; nitrates were not reduced; indole was not formed, and urea was not split.

This strain was compared by guinea pig inoculation with one of P. aeruginosa which was isolated as a non-pathogenic contaminant from a different patient. The pathogenic strain was found to be no more virulent for the guinea pig than was the non-pathogenic strain.

Comment. As mentioned in the introduction Pseudomonas aeruginosa is a not uncommon pathogen in skin and urinary tract infections, but other severe infections due to this organism are rare. It is probably because of this fact that little importance was attached to the presence of Pseudomonas aeruginosa in pure culture in the peritoneal cavity and gallbladder bile of our patient almost 2 months before death. Only when blood culture revealed a septicemia due to this organism, 2 weeks before death, was the causal relationship of the bacillus appreciated. Streptomycin was administered prophylactically in reasonable dosage during each of the postoperative periods, but the organism was found to be practically insensitive.

This suggests two possibilities: either the organism was insensitive to streptomycin from the onset, in which case valuable time was lost by using an ineffective drug, or the organism developed tolerance. If the latter was true, early treatment with massive doses of the drug might have been effective. In either case, the failure to appreciate the causal relationship of Pseudomonas to the disease resulted in therapeutic failure. The acquisition of resistance cannot be over emphasized in considering selection of the most effective drug or agent in ample dosage. It is possible that bacteriophage might have been effective had it been tried before the onset of septicemia and endocarditis. Finally, one or more of the operations might have been avoided had the presence and nature of the infection been recognized earlier.

We believe that, after exclusion of skin contamination, a culture which is positive for Pseudomonas obtained from any patient with a febrile illness should prompt the following studies: (1) A blood culture, (2) Serum aggultinins for Pseudominas (a titer of 1:30 or higher is significant)[5], (3) The sensitivity of the organism to the available therapeutic agents.

Initial dosage should be sufficiently high to prevent the development of resistance of the organism to the agent employed. In the event that the organism is not sufficiently sensitive to streptomycin or penicillin it may be desirable to prepare and administer a specific bacteriophage. Stock Pseudomonas bacteriophage might be found to be of value while awaiting preparation of the autogenous phage.

Nine other instances of endocarditis due to Pseudomonas aeruginosa have been reported[5]. In only one of these was the aortic value involved. In our case, the second showing aortic valve involvement; the organism attacked a valve which appeared to be otherwise normal.

The victims of severe or generalized Pseudomonas infections are usually debilitated, chronically ill and mal-

nourished. In contrast, this patient was in good health until the onset of his infection. It is likely that the gastro-intestinal tract was the portal of entry and that spread to the liver and pancreas ensued. The liver abscesses probably represented the foci from which the septicemia and endocarditis were derived. The relationship, if any, between this patient's disease and his accident and hematemesis is not clear.

Of particular interest is the pronounced plasma cell reaction in all lesions, indicating a process of relatively long duration as indeed is suggested by the history. Neutrophils predominated in only a few of the lesions. Although plasma cells characterize chronic infections, the number of these cells, and the prominence of young forms is unusual.

Summary. A case is reported of protracted sepsis by Pseudomonas aeruginosa (B. pyocyaneus) with lesions in many organs, and massive acute endocarditis involving the aortic valve.

Only one other reported case of endocarditis of the aortic valve caused by P. aeruginosa has been found in the literature.

The portal of entry in this case appears to have been the gastro-intestinal tract. From this locus spread occurred to the gallbladder and liver. Abscesses in the latter probably acted as foci for general dissemination of the organism.

The importance of a blood culture positive for P. aeruginosa is emphasized, and suggestions are made for further diagnosis studies.

It is essential that prompt treatment be instituted with a drug of proved effectiveness in adequate dosage in order to prevent the development of drug resistance on the part of the micro-organism.

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FURTHER CLINICAL OBSERVATIONS ON THE USE OF DIBUTOLINE, A NEW ANTISPASMODIC DRUG

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Since our preliminary report[1] on the clinical use of dibutoline (dibutyl urethane of dimethyl ethyl-β-hydroxy ethyl ammonium sulfate, Merck), we have had the opportunity of employing this drug in the treatment of many more types of cases exhibiting smooth muscle spasm. Its efficacy as a therapeutic agent in problems of spasticity of the gastrointestinal tract, the biliary tree, the urinary system and the uterus has been clinically observed and will be reported herein.

Swan and White[3] described the synthesis of dibutoline and its use as a cycloplegic and mydriatic. We had previously found this drug useful as an antispasmodic agent, either as the sole therapeutic measure or as an adjuvant, in the treatment of 3 cases of chronic, nonspecific ulcerative colitis, 2 cases of premenstural cramps, colonic spasm in 4 patients and 1 case each of duodenitis with associated spasm, functional pylorospasm and pylorospasm associated with duodenal ulcer.[1]

Pharmacological Action. Dibutoline has been shown to possess a direct inhibitory action on the smooth muscle of the intestine as well as an anti-acetylcholine or atropine-like action.[2] Peterson and Peterson[2] have demonstrated that in the normal human stomach, dibutoline inhibits the motor activity; higher doses of the drug also decrease tonus.

In clinical usage the drug generally has a qualitative action similar to that of atropine, although certain differences have been observed and will be commented upon. However, distinct quantitative differences between the two drugs have been apparent. First, the pharmacological effects of dibutoline have been observed to occur more quickly than with atropine; in from 1 to 3 minutes after subcutaneous administration effects of dibutoline are noted. Second, a more intense action is effected with dibutoline, but which has a shorter duration than the milder action of a comparable dose of atropine. An analogy may be made in comparing the quantitative actions of dibutoline and atropine to the pharmacological effects of amyl nitrite and sodium nitrite; the former acts almost immediately and with great intensity as compared with the less intense and more persistent effects of sodium nitrite.

Inhibition of Gastric Secretion. *Dogs.* In 10 tests on 5 dogs with pouches of the entire stomach dibutoline in a dose of 10 mg. administered subcutaneously

produced an average inhibition of 44% in the output of hydrochloric acid in response to 0.5 mg. of histamine dihydrochloride in a two-dose histamine test. The dogs averaged 10 kg. in body weight so that this represented a dose of about 1 mg./kg. of dibutoline. For comparison 1 mg. of atropine sulfate tested in a similar manner in the same dogs produced 56% inhibition. Therefore we may conclude that dibutoline in a therapeutic dose produces

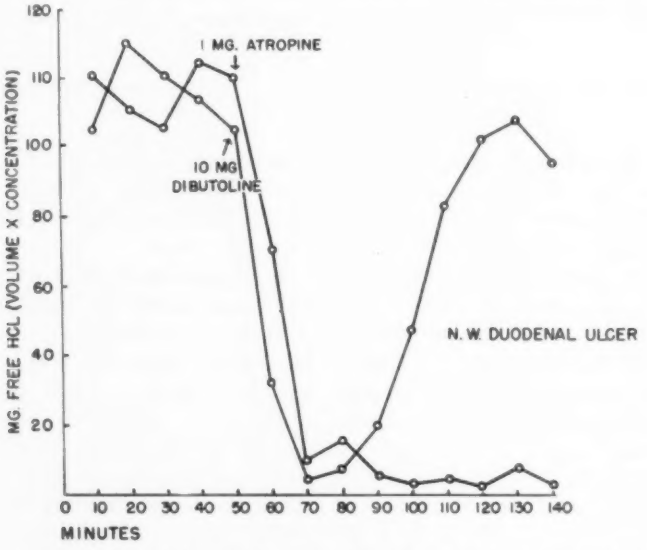

Fig. 1.—Comparison of the inhibitory effect of dibutoline and atropine sulfate on the basal gastric secretion in a duodenal ulcer patient.

almost as great a depression of gastric secretory response to histamine as does atropine in its therapeutic dose range. For both atropine and dibutoline substantial increase in the dose (for example, 50 mg. dibutoline or 3 mg. of atropine) results in only a slightly greater degree of inhibition than the smaller doses. Thus the inhibition produced by these drugs is always partial.

Man. Dibutoline (10 mg. subcutaneously) has been administered to 5 patients with peptic ulcer while the gastric secretions were being continuously drawn off by means of a Rehfuss tube. After 6 ten-minute samples had been collected to establish the basal level of gastric secretion for each patient, dibutoline was given and the gastric drainage was continued for 1 to 2 hours. In these same patients a similar test was performed either 1 week earlier or 1 week later, using 1 mg. atropine sulfate instead of dibutoline. In general the response to dibutoline was similar to that of atropine but of distinctly shorter duration. With atropine the maximal depression was still present when the test was terminated 1½ hours after administering the drug, whereas with dibutoline the secretory rate had returned to the control level within one hour. In 3 cases both dibutoline and atropine produced complete suppression of free acid secretion and in the other two patients both drugs produced marked but incomplete inhibition of acid secretion. A typical example of the latter type of response is shown in the accompanying graph (Fig. 1).

Vascular Effects. In no patient have we observed a distressing tachycardia

following the subcutaneous injection of 10 or 20 mg. of dibutoline. A moderate tachycardia of short duration may occur following the use of doses larger than 10 mg. Capillary nail bed measurements in 3 normal human subjects have revealed no significant calibre change of the loops after subcutaneous administration of 10 or 20 mg. of the drug. No appreciable alterations in arterial blood pressure have been noted in human subjects after similar dosages. Cardiac output or coronary blood flow studies have not been made. Flushing has been noticed in only 4 patients receiving dibutoline.

Clinical Observations. Dibutoline has been employed as the sole therapeutic agent or as an adjuvant in treatment of the diseases listed below.

Diseases of the Gastrointestinal Tract. 1. *Colonic Spasm.* Nineteen cases of so-called functional spastic colon have received dibutoline in doses of 10 to 20 mg. subcutaneously as the sole therapy. Complete relief of their pain was afforded to all in from 1 to 10 minutes. The duration of relief varied greatly, in some instances lasting for several weeks and in others for 2 or 3 hours. One patient required 10 mg. every 4 hours day and night for several weeks. Another, was admitted to the hospital because of his severe colicky abdominal pain plus the presence of a 3 cm. hard, movable mass in the left, lower abdominal quadrant; X-ray diagnosis of this lesion was an obstructive, intraluminal growth of the sigmoid, probably malignant. He was given 10 cc. of dibutoline subcutaneously and after 90 seconds the patient experienced a dryness of the mouth followed in 2½ minutes by cessation of the pain and disappearance of the mass as determined by abdominal palpation; the latter observation was confirmed by a barium enema X-ray study.

2. *Diverticulitis of the Colon.* The abdominal pain associated with diverticulitis has been relieved in all of 3 patients treated with dibutoline. Maintenance of freedom from abdominal pain was accomplished by using the usual 10-mg. dose 3 to 8 times daily.

3. *Chronic, Non-specific, Ulcerative Colitis.* Dibutoline has proved an important adjuvant in the treatment of all 6 cases of chronic ulcerative colitis in which it has been tried. It assists both in controlling the abdominal discomfort and in lessening the frequency of defecation. In one case 10 mg. of dibutoline given thrice daily was more effective than atropine gr. 1/50, administered at like intervals, in alleviating the abdominal pain and lessening the number of stools. In still another patient 20 mg. of dibutoline injected every 3 hours resulted in a stool-free period of 11 hours as contrasted to passage of 5 stools during an equal period when given powdered opium gr. iii orally every 3 hours over a 2-day period.

4. *Acute Gastroenteritis.* Fifteen cases of acute, severe gastroenteritis of undetermined etiology were treated with dibutoline in the usual 10-mg. subcutaneous doses repeated every 2 to 3 hours when necessary. Cessation of the vomiting and colicky pain resulted, as well as lessening of the frequency of defecation.

5. *Regional Enteritis.* Colicky pain associated with 1 case of chronic regional enteritis with external fistual formation was relieved by injection of 10 mg. of dibutoline 4 times daily.

6. *Pylorospasm Associated with Duodenal Ulcer.* In all 24 cases of typical pylorospastic pain associated with X-ray proven duodenal ulceration treated with dibutoline in 10 mg. doses complete relief was afforded; this alleviation of pain persisted for from 2 to 24 hours after a single injection and occurred in from 2 to 10 minutes after the injection.

Case Report. Case 1. A typical case

summary: A 47-year-old male was admitted to the hospital because of persistent, severe cramp-like pain in the epigastrium. He had been under treatment for recurrent duodenal ulcer for about 20 years. X-ray revealed a large crater in a spastic scarred duodenal bulb. Dibutoline, 10 mg. 4 times daily, afforded complete relief. Pain returned if a dose was omitted; atropine sulfate gr. 1/50 gave only partial relief.

7. *Functional Pylorospasm.* Ten patients with epigastric pain and vomiting with no demonstrable gastric or duodenal lesions were relieved by 10-mg. doses of dibutoline. Included in this group were 3 patients who had abdominal malignancies and whose nausea was adequately controlled without the use of narcotics.

8. *Pylorospasm Associated with Chronic Antral Gastritis.* Frequent vomiting and feeling of epigastric fullness were adequately relieved in 2 patients with chronic antral gastritis when dibutoline was given in 10-mg. doses every 4 hours.

9. *Peptic Ulcer Pain.* The typical ulcer-type epigastric distress occurring when the stomach is empty was relieved in 2 to 5 minutes after the injection of 10 mg. of dibutoline in 10 patients with X-ray proven duodenal ulcer. Not all patients with ulcer pain were so relieved, however. Such relief has also been noted clinically after atropine therapy.

10. *Pyloric Obstruction Associated with Duodenal Ulcer.* Three cases of pyloric obstruction all exhibiting marked degrees of duodenal narrowing and crater formation by X-ray and complaining of a feeling of epigastric fullness and frequent vomiting were rendered asymptomatic after the institution of dibutoline therapy consisting of 10 to 15 mg. of the drug injected subcutaneously from every 4 to 24 hours.

Case 2. A summary of a typical case follows: A 30-year-old male with a history of recurrent duodenal ulcer for 7 years complained of a marked sense of epigastric fullness and vomiting, 1 to 4 times per week, for 15 months. X-ray showed food residue in the stomach, 50% retention after 6 hours and a marked duodenal bulb deformity. Dibutoline, 15 mg., was injected once daily and within a few days the patient felt improved. The daily injections of the drug have continued for 8 months and during this time the patient has been asymptomatic, has not vomited once, has gained 15 pounds in weight and has required no other medication except dibutoline. X-ray examination done 2 months after beginning dibutoline revealed the duodenal bulb deformity but no delay in gastric emptying time.

11. *Tabetic Gastric Crisis.** The nausea, vomiting and abdominal pain associated with 2 cases of lues of the central nervous system were treated with 10- and 15-mg. doses of dibutoline. If symptomatic relief was obtained, it was only slight and transient.

12. *Infantile Pyloric Stenosis.*† Prompt and spectacular relief from the food regurgitation present since birth plus gain of 7 ounces weight in 4 days was afforded an 8-week-old infant by administration of 3 mg. of dibutoline 10 minutes before each feeding. A subsequent surgical procedure revealed the hypertrophic pyloric sphincter. In 3 cases of infantile pyloric spasm subsequently observed, dibutoline was found to afford only slight or equivocal relief.

Gastro-Intestinal X-ray Observations. Observations on the effect of dibutoline have been carried out in connection with clinical radiological work on normal individuals and on patients. Cases selected included instances of long de-

* For the excellent observations in these 2 cases we are indebted to Drs. E. E. Peters, J. Rodrigues and B. G. Clarke of the Chicago Intensive Treatment Center.

† We wish to express our appreciation to Drs. Harry Tarre, J. B. Richmond and B. G. Clarke of Cook County Hospital for data in this case.

lay in the opening of the pylorus, especially where the delay was accompanied by demonstrable spasm of the prepyloric zone for distances of from 2 to 5 centimeters. Cases were also chosen where in giving the opaque enema a high grade of spasm was encountered in the distal colon. The dose administered was always 1 cc. (10 mg.) subcutaneously.

Some difficulty in the assessment of the results should be noted. It is a matter of common observation among radiologists that one often finds the first swallow of barium traversing the stomach and without any appreciable delay immediately passing into the duodenal bulb; in other cases a delay occurs, with no barium passing through the pylorus. In the latter event, various things may happen. In the usual case it may be observed that when one of the peristaltic waves approaches to within 3 or 4 centimeters of the pylorus, the latter opens and the duodenal bulb fills, to remain filled or to contract almost immediately with onward passage of part or all of its opaque contents. This may occur after watching only 1 or 2 minutes, or after a longer vigil the observer's patience may be strained and he may try a little manipulation with the palpating spoon or the protected fingers under the screen to slip some of the barium from the ampulla through the pylorus into the duodenum. This massage-like maneuver may succeed but in other cases it seems to set up even more stubborn tightening of the pyloric sphincter, with no barium passing into the duodenum. In other cases the radiologist may draw a word-picture, more or less eloquent, of a savory meal being eaten under pleasant surroundings. In most cases the stomach almost immediately will begin active peristaltic waves and within a few seconds pass material into the duodenal bulb. But there are instances in which all of these maneuvers fail, and then one must seek some further means of visualizing the duodenal bulb.

Ordinarily atropine sulfate has been employed, beginning with a dose of 1/75 of a grain. One of us (J.T.C.) once gave 1/75 of a grain of atropine sulfate to 1000 consecutive gastrointestinal cases 30 to 45 minutes before the barium meal study was commenced. This was done because of the relatively large number (10 to 15%) of gastroduodenal studies where reexamination was requested to eliminate as far as possible any influence of pylorospasm. No untoward effects were observed in any of these 1000 cases which included young and old of both sexes, but it was noted that unless the atropine sulfate was given to full physiological effect, sometimes requiring 1/30 of a grain, the antispasmodic benefits were not assured. It may be that the same is true of dibutoline, for we observed variations of its effects.

In otherwise normal individuals who were exhibiting pyloric spasm, dibutoline usually had the effect of relaxing the spasm; so that whereas up to the moment of making the intramuscular injection nothing had passed into the duodenal bulb or beyond, within 3 to 5 minutes after the injection the barium mixture passed readily and spontaneously into the duodenum.

Sometimes the effect is not so prompt. In one case, repeated observations over a period of fifteen minutes from 10:30 to 10:48 revealed that no appreciable amount of contrast material passed into the duodenal bulb (Fig. 2a). At 10:48 dibutoline was injected. At 10:57 the bulb was beginning to fill. By 11:18 it was well filled and barium was beginning to enter the jejunum (Fig. 2b). At 1:15 the stomach was just emptying its last traces and the distribution of barium through the small bowel was normal.

There were, however, cases in which

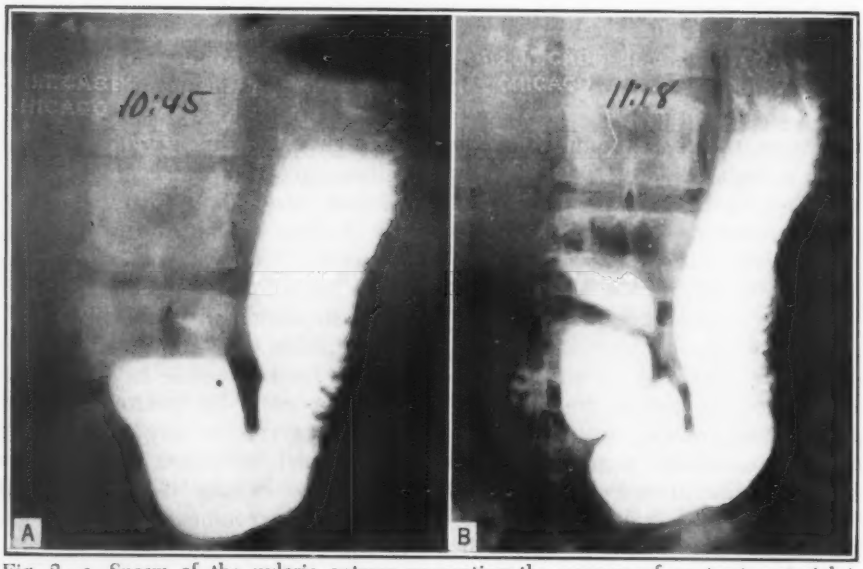

Fig. 2.—a. Spasm of the pyloric antrum preventing the passage of contrast material into the duodenal bulb.
b. Stomach of same patient 30 minutes after the subcutaneous injection of 10 mg. of dibutoline. The bulb is now well filled.

Fig. 3.—Atonicity and lack of peristaltic activity 10 minutes after the subcutaneous injection of 10 mg. of dibutoline.

the dibutoline seemed to have the opposite effect. In stomachs which showed no spasm or hyperperistalsis, the administration of dibutoline seemed to cause a slowing down of the motor process with almost complete cessation of its activity, this occurring within 30 minutes. This was noted for a period of about 1 hour, during which time there was a notable lack of passage of opaque materials into and along the small intestine. Then the

rate of transit of the opaque material became much more rapid and resembled the normal behavior.

In another case, during 20 minutes of observation nothing passed the pylorus, and we were unable by any maneuver to get anything into the duodenum. Dibutoline was injected and the bulb appeared spontaneously within 5 minutes but remained rather spastic and the stomach itself showed normal tonicity for about 5 minutes after which there supervened a period of atonicity, the stomach presenting instead a lack of peristaltic activity and the general aspect of gastrectasis (Fig. 3). Then there was a gradual resumption of normal peristaltic activity, so that within another half hour the active peristalsis had nearly emptied the stomach.

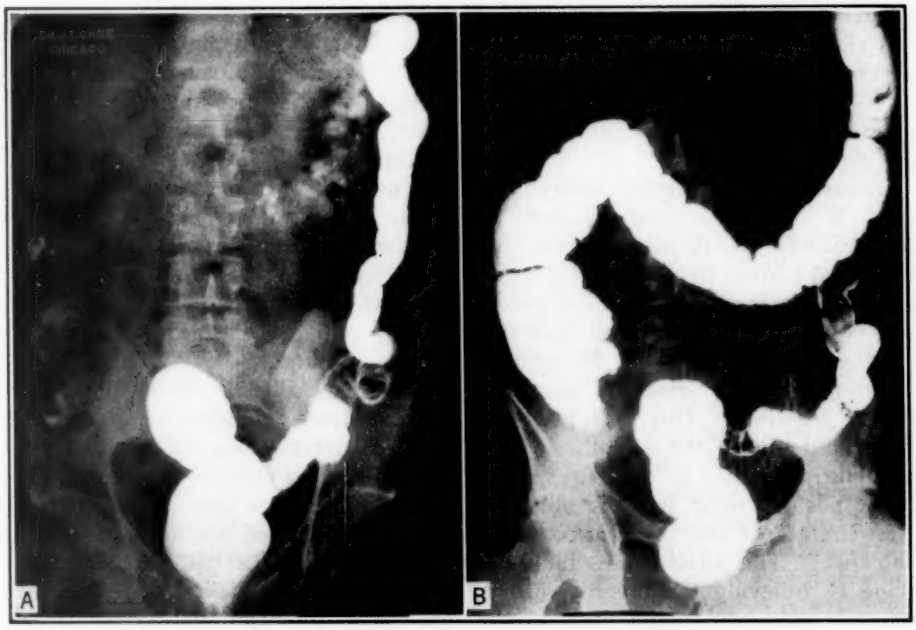

Fig. 4.—a. Incomplete filling of the colon due to generalized spasm.
b. Colon of same patient 20 minutes after the subcutaneous injection of 10 mg. of dibutoline. Complete filling is now easily accomplished.

In another case, (Fig. 4a) the complete filling of the colon by the opaque enema was found impossible. After much coaxing the patient had been persuaded to accept enough of the contrast enema to visualize the colon as far as the splenic flexure. He then rebelled and it became quite obvious that he could not take any more. He was studied in various projections to ascertain that there was no obstruction of any kind at the splenic flexure to impede the progress of the barium through the colon. Obviously it was a case of intense colonic spasm. He was allowed to expel the enema, and returned to the table with the colon practically clear. Ten minutes after injection of dibutoline the enema was repeated. This time not the slightest difficulty was encountered in filling the entire colon over to the ileocecal value (Fig. 4b).

Diseases of the Biliary Tract. 1. *Gallstone Colic.* Only 1 case of gallstone colic was treated with dibutoline. This patient was relieved completely

of pain 5 minutes after a 10-mg. injection of the drug. Atropine sulfate, gr. 1/75, had no effect in similar attacks in this patient.

2. *Biliary Dyskinesia.* A presumptive diagnosis of motor dysfunction of the gall bladder and sphincter of Oddi (not confirmed by visualization of the hepatic ducts during cholecystography) was made in 1 patient complaining of recurrent attacks of nausea, vomiting and right upper abdominal pain with interscapular radiation. Dibutoline in 10-mg. doses afforded this patient complete relief, while 1/50 grain of atropine sulfate did not.

Diseases of the Genito-Urinary System. 1. *Dysmenorrhea.* Relief of pain was afforded 10 patients with premenstrual cramps by 10 mg. of dibutoline. However, as had been our previous experience, little benefit was derived from dibutoline in 10 women experiencing pain after the onset of uterine bleeding. This observation lends credence to the hypothesis that premenstrual pain is due to spasm, while post-bleeding pain is not.

2. *Ureteral Colic Associated with Calculus.** The effectiveness of dibutoline in relieving the severe pain of ureteral colic in patients with stones has been variable. We believe the failure of treatment of some of these cases is due to inadequate dosage of the drug. Six cases of X-ray proven ureteral calculus were given 10 to 30 mg. of dibutoline and 3 of these were afforded complete relief of their pain without the supplementary use of narcotics or analgesics. The remaining 3 cases, however, required additional morphine sulfate for control of pain. In the successful cases pain was controlled by using 10 to 30 mg. of dibutoline every 3 to 8 hours; all 3 of these patients passed their stones spontaneously during treatment.

3. *Bladder Spasm following Cystoscopy and Transurethral Prostatic Resection.* With 1 exception, post-manipulative of post-operative pain after cystoscopy was controlled by dibutoline alone in 22 cases. No analgesics and no narcotics were necessary. The usual regimen consists of giving 10 to 20 mg. of the drug immediately before introduction of the cystoscope followed by a similar dose immediately after completion of the procedure.

4. *Cystitis.* The pain incident to infection of the urinary bladder was completely relieved by 10-mg. doses of dibutoline in 2 cases. In another like number of patients, however, sufficient relief was not afforded to warrant withholding analgesics.

5. *Suprapubic Prostatectomy.* Relief was given 3 post-operative prostatectomy patients by the use of 10 to 20 mg. of dibutoline every 2 to 3 hours. It was found, however, that the effect of dibutoline was enhanced by using a constant intravenous infusion of 5% ethyl alcohol solution. When these 2 medicaments were used simultaneously immediately after the operation, the relief afforded the patient was such that no opiates were necessary during the entire post-operative course.

Side Effects. The common side reactions to dibutoline treatment are dryness of the mouth and diminution of ocular accommodation. The dryness of the mouth usually lasts from 20 minutes to 1 hour and is considerably less distressing than that which follows atropine therapy. As was mentioned previously, we have not noted a significant tachycardia or alteration in the arterial blood pressure in any case in the doses of the drug used (3 to 30 mg.). Flushing of the skin has been observed in several patients. As much as 30 mg. have been injected subcutaneously with no other than the

* We are indebted to the members of the Drs. V. J. O'Connor-K. Sokol G. U. service of Wesley Memorial Hospital, Chicago, for their cooperation in obtaining the results of dibutoline on urinary tract diseases.

effects noted above. One patient has received from 80 to 100 mg. of dibutoline daily in divided doses for as long as 2 months and has manifested only moderate dryness of the mouth and minimal visual disturbances. Three other patients have tolerated equally well 40 to 60 mg. per day for periods up to 3 months.

Dosage. The usual subcutaneous dose for adults is 10 mg. If no relief is obtained in 20 to 30 minutes, it has been customary to repeat the dose followed by injection of 10 mg. as needed symptomatically. The duration of action of the drug judged by clinical standards of patient comfort varied from 1 to 24 hours or longer. Occasionally in cases of severe spastic pain we have commenced treatment with 20-mg. dosage and repeated this amount as needed.

The drug has not been administered intravenously in human subjects. It has proved ineffective when given by mouth; no effect has been observed when as much as 1500 mg. has been taken orally.

Clinical Value. We believe that dibutoline has a place in the therapy of spastic disorders of the gastro-intestinal biliary and genito-urinary systems. Its usefulness is enhanced by intensity and promptness of its effect, a property not possessed by atropine. When almost immediate, powerful anti-spastic action is desired, dibutoline, on the basis of our experience, will accomplish this. The drug has also proved useful to the roentgenologist in combating spasm of the pylorus and antrum and the colon in gastro-intestinal X-ray visualization.

In many instances a single dose of the drug provides relief for a period which far exceeds the duration of its pharmacological activity. This would indicate that in these cases once the spasm is relieved it does not recur immediately even though no drug is acting to prevent it. In the instances where this is not true the recurrence of pain may make quite frequent administration of the drug necessary; in extreme cases as often as every 2 hours. Inasmuch as the drug is only active by parenteral routes, this entails the inconvenience of repeated injections. The failure of the material to be active by the oral route seriously limits its use in ambulatory patients in whom it would otherwise be indicated.

Summary. Dibutoline, possessing both a smooth muscle inhibiting and an anti-acetylcholine action, has been employed as the sole therapeutic agent or as an adjuvant in the treatment of smooth muscle spasm associated with 12 types of disorders of the gastro-intestinal tract, 2 of the biliary tract and 5 of the genito-urinary system. The results have been most favorable with the exception of the treatment of gastric crisis associated with tabes.

The drug has proved useful in combating spasm of the upper gastro-intestinal tract and the colon during the course of X-ray examination.

Side effects of dibutoline have been mainly moderate dryness of the mouth and slight diminution of ocular accommodation following the usual 10- to 20-mg. subcutaneous dosage.

The drug has proved exceedingly useful when a prompt, powerful antispasmodic agent is indicated. The short duration of its action and its ineffectiveness orally limit its usefulness.

Addendum: Since submitting this report for publication, we have used dibutoline in the treatment of about 3 times as many cases of spasm as described herein with comparable results.

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PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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PROGRESS AND DEVELOPMENT OF ANESTHESIA IN THE UNITED STATES

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THE importance of the discovery of anesthesia for the relief of pain during surgical procedures is universally recognized as one of the major advances in surgery. Without anesthesia, surgery would be limited indeed. It is not the purpose of this paper to review the differences in surgery of the preanesthetic period with that of today. A discussion of the progress and development of anesthesia, however, must take into account the advances that have been made in this field not only in the development of drugs, but in the opportunities for training of personnel and the development of anesthetic agents and technics. That in recent years there has been improvement in anesthesia is a well accepted fact; that progress is continuing in the field of anesthesia is evident and there appears to be still room for improvement even without the addition of new drugs. The final index of progress must be judged by whether an ever increasing number of patients receives better and safer anesthetic management not just next year, but for years to come. It is important, therefore, to discuss the subject of anesthesia not only in relation to drugs and methods of procedure, but also in relation to the development of personnel.

The development in the management of pain relief for surgery may be arbitrarily divided into 3 periods. First, the latter half of the nineteenth century after 1846; second, the first quarter of this century; and third, from the end of the first quarter of this century to the present time.

The period immediately following Morton's successful demonstration of ether anesthesia was notable for the rapidity of acceptance of this new procedure. Thus, relief of pain and the horror of surgery was hailed as a turning point in surgical treatment. In those early days, surgeons were recognized because of their ability and judg-

ment and not by their tools, but there was no such recognition for the administrator of anesthesia. The controversy about prior rights in the use of ether as an anesthetic agent caused much conflict but no leader in the training of the anesthetist or an evaluation of the effects of anesthesia was forthcoming. It is regrettable that under such a state of affairs the progress and development of anesthesia was slow in America. Fortunately, with physicians following the influence and prestige of John Snow[28,39] in England, there were many contributions from that country, and his work was frequently quoted in American literature[17,64,66,71].

We owe much to the dentists who became interested in anesthesia during the early period; they were mainly responsible for the early use of nitrous oxide and apparatus for its administration. Both Morton and Wells were dentists and this, no doubt, prompted the interest of others in their profession to take up anesthesia. There was no infiltration anesthesia then and restorative dentistry did not save as many teeth from extraction as does present-day dental care.

The drugs introduced and their methods of administration that originated during this first half century are of paramount importance and most of them are still in use; the same is true of the technics used at the end of this period, with some improvements.

Fortunately fate, plus Morton's persistence, determined that ether should be the first inhalation drug. Ether has many desirable properties as attested by its present-day use. The importance of this drug in the first century of anesthetic development is probably generally underestimated. It has been administered to millions of patients under every possible circumstance as to the operation, surgeon and administrator. We do not know how many anesthetic deaths have resulted from its use, and if we did, one could not judge how well it was administered or how many more deaths might have occurred with another drug. The fact that it is still widely used for anesthesia is good evidence of its value.

Wells had been working with nitrous oxide to produce pain relief as early as 1844, but had not succeeded in convincing anyone of sufficient professional standing to have the idea accepted. This drug has a very low potency and is the only inhalation drug used that is not a hydrocarbon. In spite of the lack of potency, nitrous oxide is very widely used for induction of anesthesia and used with more potent inhalation and with nonvolatile drugs. Throughout the many changes in anesthesia, nitrous oxide continues to maintain some usefulness in nearly every operating room in this country.

Simpson's advocacy of choloroform in 1847 was of importance and it was widely used in this country only during this early period. Its one dangerous property, namely its propensity to disturb cardiac function if not administered with extreme care, still makes it unsafe for common use. It was used extensively in this country during this period and most writers recognized that it was not as safe as ether, particularly for the many unskilled individuals who were administering anesthesia[4, 63].

The use of ethyl chloride was perhaps of less importance but it is still used for inhalation anesthesia; Snow is supposed to have used it in 1851[38]. Rice says it was first used by Heyfelder in 1848 but never extensively until 1895, when a more purified drug was available[56]. The introduction of the use of oxygen with nitrous oxide by Andrews[5] was a valuable contribution. Snow used amylene and reported some 238 administrations, but it was not used by others as far as is known and is only of historical interest[38].

The use of nonvolatile drugs, by mouth, to relieve pain is centuries old

but the administration of morphine, subcutaneously and intravenously, was made possible by the invention of the hollow needle by Wood in 1853. This needle with the proper syringe set the field for local and regional anesthesia.

In 1860, Albert Nieman[39], of Germany, isolated the alkaloid cocaine in crystalline form and reported the numbing effect on the tongue. Corning experimented with spinal anesthesia and it was accomplished in humans at the end of the century by Bier[10] of Germany. Matas[44] was one of the first to work on this problem in this country. The topical use of cocaine in the eye was introduced by Koller[39] in 1884. The injection of nerves and tissues with cocaine to produce local and regional anesthesia was performed near the end of this period by Cushing and Halstead[39], and also by Crile as reported by Matas[46].

Apparatus for the administration of inhalation anesthesia was well on the way to furnish a background for later development. Oxygen and nitrous oxide were compressed in metal cylinders. The principle of rebreathing volatile drugs was employed, though not highly developed. Squibb[62] and Prince[55] advocated allowing adequate air with ether and this culminated in real open-drop technic.

The practice of keeping records during anesthesia was started by Codman and Cushing[8]. Blood pressures were taken with the Riva-Rocci sphygmomanometer as introduced into this country by Cushing[30] These pressures were recorded on a graphic record before, during and after operation. However, it remained for a later publication[50] to convince the anesthetist of the value of such records.

The second period, 1900 to 1925, was filled with tremendous advances in all scientific fields, including anesthesia. While the development and improvement in technics and practices from the previous period were of signal importance, many new anesthetic agents were discovered.

The most important class of drugs introduced was the synthetic nonvolatile cocaine substitutes to be used for blocking nerve impulses, commonly called local, regional and spinal anesthesia. The first of these to be used extensively was stovaine, synthetized in 1903. In 1904, Einhorn synthetized procaine which replaced stovaine and remains one of the most widely used drugs for conduction anesthesia. The use of local as well as spinal anesthesia played an important part in interesting the profession in anesthesia; it gave opportunity and necessity for surgeons to become concerned with this field. Many minor surgical procedures could be performed with local infiltration much more safely than with poorly administered general anesthesia. Epinephrine, discovered in 1897[1], came into use as a vasoconstrictor in combination with local anesthesia in this period. Ephedrine, described as a vasopressor drug by Chen and Schmidt[14], was later employed in conjunction with spinal anesthesia.

Ethylene, introduced by Luckhardt[42], was the only important addition to the inhalation anesthetics during this period. Its discovery stimulated further search for inhalation drugs.

The introduction of new technics also received a large amount of attention. Herb[33] states that Prince advocated using an open mask for ether and this method was widely used in this period as an improvement over the use of the closed cone. Prince modified the Esmarch mask to make the best open ether mask[54]. The intralaryngeal insufflation for open chest was described by Matas[45]. Kuhn's intratracheal tube was reported by Hazelhurst[31]. The work of Meltzer and Auer[47] led to the development of intratracheal insufflation[19], which, in turn, was a forerunner of present-day endotracheal airways, which in this country was described by

Janeway[36] in 1913. This technic was developed largely by the English anesthetists, Magill and Rowbotham[58,59]. The latter was a very important contribution because the most troublesome and dangerous complication of all general anesthesia is respiratory obstruction. The use of the endotracheal airway, which consists of a tube of sufficient size to permit breathing through its lumen, has been a most valuable feature in rendering safer and better anesthesia with greater convenience to the surgeon. The history and development of this type of airway is very capably presented by Gillespie[24].

Spinal anesthesia was well understood and used by some during this period but not widely. This work, interestingly enough, at the early stages, was done mostly by surgeons; one of the outstanding being W. W. Babcock.[7] The professional anesthetists' time probably was consumed administering inhalation anesthesia or perhaps they were not interested in spinal anesthesia at that time.

Inhalation apparatus was improved. Rebreathing technic was worked out carefully by Gatch[23] McKesson developed the intermittent flow valve[48]. The carbon dioxide absorption technic was introduced as a laboratory procedure by Jackson[35] and for clinical anesthesia by Waters[67]. However, the introduction of this apparatus did not simplify anesthesia but actually added responsibility for the anesthetist, because the patient must live on the atmosphere made by the anesthetist in contrast to the open drop, where ether is added to atmospheric air breathed by the patient. In spite of the high oxygen concentration possible with ether and the carbon dioxide absorption technic, there is a respiratory hazard of inadequate pulmonary ventilation that may be overlooked because of the good color of the blood and often absence of any marked changes in circulation until late in the sequence of events that may lead to severe complications. The use of an artificial atmosphere may be hazardous therefore, if one does not have a proper understanding of physiology of respiration.

McKesson's report is both an excellent discussion of the physiology of circulation during anesthesia, and a demonstration of the importance of keeping a graphic record of the patient's condition. It so stimulated others[49,50] that by the end of this period adequate records were kept by most professional anesthetists. Further development of this phase of anesthesia came in the next period as part of the improved teaching program.

A summary of the progress in anesthesia during this period is striking for the many advances in the knowledge of drugs, technics and the management of the patient. Spinal, nerve block and local anesthesia were highly developed. Inhalation methods were improved and at the end of the period the carbon dioxide absorption technic was in practical use. The use of endotracheal airways was well established and found increased use in the next period.

During the more recent period (1925-48), many new drugs were added without discarding the old ones, but Squibb's statement is still as true as it was in 1871; "Time, that tries all things, has disposed of many of the issues which arose in the early application of anaesthesia, but has entirely failed in producing that universally applicable anaesthetic—that philosopher's stone for which the alchemists of the profession still vainly search—namely, an agent which shall be potent, but potent only for good. This physical impossibility seems to be to the medical profession what perpetual motion is to mechanics, and time wears away such heresies very slowly. It would, doubtless, be better for the profession and for mankind if the anaesthetics already known were better studied in relation

to their special adaptations, and were applied with a more wise discrimination"[64].

There had been interest in intravenous administration of anesthesia for some years and, with the introduction of pentothal sodium, this type of anesthesia became very useful. It has been well discussed by Adams[2]. It has the advantage of producing unconsciousness rapidly and pleasantly with a minimum of after effects that are remembered by the patient. Its limitations and disadvantages in producing good surgical anesthesia if used alone are now recognized. It is rarely used as the only drug where relaxation, prolonged time and debilitated patients are involved, because it does not block certain spinal reflexes with the amount of depression tolerated under these conditions. The ease of intravenous injection may lead unqualified administrators to misuse the drug. The failure to remember that the production of unconsciousness with any drug places severe responsibility on the administrator may lead to trouble, especially in office practice and when done by those not familiar with preventing and treating the possible complications of this state. The discovery by Griffith[28] that curare preparations could be used and controlled in producing relaxation, and its further introduction into anesthetic practice by Cullen[15], has also been a helpful adjunct, through the intravenous route of administration. As with other drugs, one can only estimate the required dosage and an overdose must be treated by artificial pulmonary ventilation. Its proper use produces good muscular relaxation with lesser concentration of other drugs. It has also been employed to control convulsions and muscle spasm[61].

The intravenous use of procaine hydrochloride to produce analgesia for labor pain and parturition was used by Allen and Crossman[3]. However the hazard of convulsions occurred often enough to discourage its widespread use. Burstein[13] used intermittent injections of procaine to treat severe cardiac depression or irregularities during cardiac and pulmonary surgery. Fraser[20] has reported the use of small amounts of procaine intravenously as an adjunct to general anesthesia, particularly to prevent cardiac arrhythmia. Bittrick[11] reported the use of large doses of procaine during intrathoracic operations. The reviewer[65] has been studying the use of rather large doses of procaine given intravenously in conjunction with other drugs that produce general anesthesia. Procaine hydrochloride 1% is given continuously in 5% glucose at a rate of 2 to 10 cc. per minute. It has been tried with several drugs; the most satisfactory has been a combination of pentothal induction followed by intravenous procaine and continuous flow of nitrous oxide and oxygen. If relaxation is necessary a curare preparation is used. The study has not been completed but some impressions have been formed: the procaine does not accumulate in the body as in the case of barbiturates; the only effect remaining after its flow is discontinued is pain relief, and consciousness returns rapidly; because of pain relief patients are not irrational but very clear mentally on recovery; the cough reflex is markedly depressed even in light anesthesia so that patients tolerate an endotracheal airway well; patients with toxic thyroid disease are benefited by procaine in that they have fewer pulse and pressure changes during operation and appear to be less disturbed during the postoperative period. These findings during anesthesia and operation have given reason to believe that intravenous procaine properly controlled might be efficient in treating thyroid crises. Postoperative pain relief is quite variable, ranging from 30 minutes to several hours. Vagovagal reflexes are depressed and per-

haps other undesirable activities of the autonomic nervous system are depressed or eliminated. This use of procaine should not be confused with the therapeutic use described by Peterson[51], because these large doses require more careful observation and control; they are not without danger the same as any other drug used in the degree necessary to produce surgical anesthesia.

The synthetic cocaine substitutes metycaine, pontocaine, nupercaine, monocaine and intracaine have been given an extensive clinical trail and compared with the old standby procaine hydrochloride. Anesthesiologists trained in their use, limitations and dangers have found the longer acting ones such as pontocaine and nupercaine of value because of this duration of action, if at the same time proper precautions are being taken against excessive circulatory depression and respiratory paralysis. Lundy[43] has discussed these drugs and the technics in detail.

Two inhalation anesthetic drugs, divinyl ether and cyclopropane, have been accepted for clinical use since 1925. Ravdin et al.[26], reported a careful laboratory and clinical study of divinyl ether. This drug produced unconsciousness rapidly and was less irritating to inhale than ethyl ether. It is chiefly used for very short operative procedures or for induction before ether anesthesia. It is not toxic to the heart, but is toxic to the liver and kidneys if given for prolonged anesthesia. It produces rather marked salivation in patients not given belladonna drugs. Cyclopropane was also studied extensively before being released for general use by Waters and his colleagues[69,70, a, c, d, e, f]. It was found to produce a pleasant induction and ample oxygen could be used because of its potency producing anesthesia in 10 to 30% concentrations in the inhaled atmosphere. It was best used with the carbon dioxide absorption technic. Undesirable post-anesthetic complications such as nausea were much less than with ether. On the other hand this drug does not depress the activity of the autonomic system as in case of ether, and certain undesirable reflexes are not well obtunded by it in ordinary concentrations such as the laryngeal and vagal reflexes. While it does not depress the circulatory system, it may disturb the automaticity of the heart with resultant cardiac arrhythmia. It cannot be safely and economically administered by all methods as in the case of ether. In order to take advantage of its desirable properties one needs to be skilled in its administration.

The introduction of these two drugs illustrates the highest degree of precaution taken before they were released for general use and displays good cooperation on the part of the manufacturer and research worker during the study and clinical trial period.

Recently a similar study lasting for a period of 8 years has been reported in relation to chloroform, with careful laboratory and clinical controls[70 b, c, e, 52]. The cardiac effects of chloroform and cyclopropane were studied on dogs. Liver and kidney function were followed carefuly on many patients receiving chloroform, cyclopropane and ether. Electrocardiographic records were taken on many hundreds of cases. In brief, the tendency of chloroform to produce liver and kidney damage is not particularly different from the many other anesthetic drugs[52]. However, its danger lies in the all too frequent serious cardiac depression. There were no cardiac deaths in over a 1000 administrations but there were instances of cardiac arrest which were corrected by prompt and vigorous pulmonary inflation with oxygen[70-a].

New technics and methods of administration, or re-introduction of old methods, have been of advantage. The Lemmon technic of continuous spinal

anesthesia[40] and its auxiliary continuous caudal anesthesia, introduced by Hingson (See Edwards and Hingson[18]), have finally settled into their respective usefulness after waves of popularity. They have added increased technical requirements and the advantage of lending control to spinal anesthesia that is of particular value in some cases, this control involving both level and duration of anesthesia. The idea of using a vasoconstrictor drug in the anesthetic solution in spinal anesthesia was revived and is now being tried widely[53] to prolong the time of analgesia of procaine and pontocaine. The effect of these drugs given intrathecally has not been found to make much difference in the blood pressure according to clinical and laboratory work done by Henderson[32].

Along with operative surgery, anesthesia has benefited much by the application of knowledge of human physiology. Even within the reviewer's experience there has been a marked improvement in preoperative care of patients. Proper use of parenteral fluids, electrolytes and blood have been highly beneficial. How one used to dread anesthetizing patients with intestinal obstruction and marked abdominal distention! With long tube decompression introduced by Abbott and Johnston[37] the anesthesia problem and hazard has been reduced. The modern operating room usually has cross-matched blood ready for every procedure that may be accompanied by considerable blood loss during operation. Blood is replaced as lost to prevent circulatory depression and shock is usually not allowed to develop.

The third period has brought new drugs, new technics, new teaching methods, new fields in therapy outside the operating theater, a new name "anesthesiologist" to replace the old term "anesthetist", new problems in economics, and we believe much improved clinical anesthesia to a larger number of patients as well as a much improved professional status for the anesthesiologist.

During the period immediately following the introduction of anesthesia the personnel involved in the administration of anesthetic agents was apparently not thought to be of much importance. In the case of the first public administration of ether, the surgeon was the key figure. Despite the fact that Morton conducted a demonstration which was obviously destined to change the course of surgery, to save lives and alleviate suffering, the remarks about the performance which we remember were those of the surgeon. If Warren's remark, "Gentlemen, this is no humbug", established the respectability of anesthesia itself, it did nothing to encourage physicians to become anesthetists. Actually data concerning individuals interested in the administration of anesthetic drugs in this early period are hard to find and more difficult to evaluate. Most of the innovations were introduced by surgeons who naturally were much concerned with anesthesia. As to the administrators of anesthesia one finds lamentations in the literature concerning the neglect of this aspect of anesthesia. In 1860, an editorial states, "The delicate and most responsible task of administering the agent is usually committed to a junior physician who has no knowledge whatsoever of the nature of his duties; he knows nothing of the different stages through which the patient is to pass or the value of the symptoms which appear during the administration"[17]. In the same year Squibb[63] wrote concerning the importance of the skill and experience of the administrator.

Inspired by John Snow, English physicians took over the administration of anesthesia in large measure and it was developed and treated as a branch of the practice of medicine. There was no such recognition of professional an-

esthesia in the United States at that time. A few men were engaged in clinical anesthesia at the turn of the century and their numbers increased in the next period. Apparently the task of administering anesthesia was the least desirable and was assigned, all too often, to the "low man on the totem pole". The importance of the administrator of anesthesia was not recognized, it provided very little remuneraion, and therefore few were found who were willing to devote the majority of their energy and interest to this phase of surgery.

The practice of utilizing an apprentice or intern for the administration of anesthesia until he was permitted to carry on what was considered more interesting activity has persisted in many places until recently. However, as might be expected, the dependability of such personnel for anesthesia caused frequent difficulties for the surgeon and gradually gave impetus to the development of personnel for anesthesia along two lines: One, the employment of physicians who spent the major portion of their time administering the anesthesia, and two, the employment of specially trained graduate nurses for this purpose.

Galloway[21], writing at the end of the century, pointed out that for the most part anesthesia was poorly taught to medical students. After a lecture from the surgeon on anesthesia, they were expected to be able to administer anesthetic agents without further supervision and perhaps no period of observation. In discussing the relationship of the "anaesthetizer" to the operating surgeon, he says, "To do his best work, the surgeon must not have the responsibility of the administration of the anaesthetic on his mind; the anaesthetizer must have sufficient skill to keep the patient in the best possible condition to facilitate the operation." He also had a well advanced understanding of proper professional respect as shown by his statement, "In private practice the surgeon or the family physician should introduce the anaesthetizer to the patient with the cheerful assurance that in this doctor's hands he need not have fear for his safety or comfort". In another publication, Galloway[22] discusses the need for a specialty of anesthesia and states his views on the importance of anesthesia, which are well ahead of the beliefs and practices of many other surgeons of his time. He made the following very interesting prophesy: "The anaesthetizer will have to make his own place in medicine; the profession will not make a place for him, and not until he has demonstrated the value of his services, will it concede him the recognition which the importance of his duties entitles him to occupy. He will be obliged to define his own rights, duties and privileges and he must not expect that his own estimate of the importance of his position will be conceded without opposition". This is an amazing prediction of the steps, trials and tribulations that the specialty and its active members have passed through since Galloway offered this information in 1899.

The present director of Anesthesiology at Flower Hospital, New York City, D. E. Brace, is in charge of the oldest department of anesthesia organized and staffed by physicians, in this country. In 1899, the late T. S. Buchanan was appointed attending anesthetist at Flower Hospital in New York. As far as I have been able to ascertain, this was the first Department of Anesthesia in a hospital and medical school with physicians designated as anesthetists. Buchanan was apparently the first professor of anesthesia when he was appointed to the Chair of Anesthesia, established at Flower School of Medicine in 1905[12]. The Hahnemann Hospital and Medical School in Philadelphia started a department of anesthesia about the same time and these departments have been staffed

entirely by professional anesthetists ever since their inception. Previous to this organization anesthesia was administered by physicians[60]. These institutions, as well as many others, have demonstrated that anesthesia can be conducted entirely by the profession without technical administrators. In 1898, Dr. T. L. Bennett[9], one of the early pioneers in the practice of anesthesia in New York, was listed under the title of Anaesthetist and Instructor in Anaesthetics, Hospital for Ruptured and Crippled, New York.

Golden[25] has written at length discussing his difficulties in maintaining his independence as a consultant in anesthesia and collecting his fees directly from the patient. It seems to have been common practice after 1900, as well as before, for the surgeon to pay the anesthetist after collecting from the patient. This allowed the surgeon to fix the fee, make profit on it if he was not honest and was another irritating means of keeping the anesthetist subordinate.

There were many essays published concerning the status of anesthesia and anesthetists. Organized teaching was started in some medical schools. Robb[57] in 1909 recommended that a medical anesthetist hold a staff appointment in the medical school to teach anesthesia to medical students, both theoretical and practical. Long [41], in 1915, declared anesthesia to be a full fledged specialty and also admitted that a problem still existed in this statement "If the administration of anesthesia were not looked upon as a trivial matter by the majority of surgeons and hospitals, and if the expert anesthetist were accorded the same recognition as a consultant, as are the men in all other specialties there would be no anesthesia problem for solution".

Improvement in personnel was the very important feature of the period from 1900 to 1925. This phase of development has been ably discussed by Waters[68], and he has paid highest tribute to F. H. McMechan for his years of capable organization and his stand for better anesthesia. The reviewer recommends all the publications presented at the Ether Centennial for reading as they cannot be improved upon for the phases which they cover[6]. There was a marked increase in the number of physicians directing their activities to anesthesia. The Long Island Society of Anesthetists was formed in New York in 1905; the first member, Erdman, is still living. This became the New York Society of Anesthetists and was later organized as the national organization (Gwathmey)[29]. With F. H. McMechan as editor, the Quarterly Supplement in Anesthesia was published in the American Journal of Surgery from 1914 to 1926. Also, Year Books in anesthesia were published in 2 volumes for 1915-16 and 1917-18. These journals contained many excellent publications by outstanding anesthetists and are recommended reading.

During this time the nurses employed by hospitals were taking an important part in anesthesia, namely, that of getting "today's work" done, which, after all, is very important. It was never intended that they would bring about scientific advances in the specialty; nor was it intended that they would delay or prevent progress; so, if the latter has happened, it was indirect and unintentional. The question arises how will this large group of nurse anesthetists fit into the next period where we can already anticipate marked changes in personnel administering anesthesia. Actually, with the rapid growth of the country with increases in population there was need for all the physicians and nurses available for any or all branches of surgery. There was ample room for an increase in numbers of professional anesthetists without changing the entire personnel problem except for constant improvements in the quality of the work.

The specialty of anesthesia, how-

ever, was not widely recognized or accepted by the medical profession until recently. Some communities enjoyed the services of anesthetists who were doctors of medicine and who devoted their full time to anesthesia; other areas had no such service. Incident to the increase in number of surgical procedures there was a marked increase in the number of nurses administering anesthesia. The remuneration was better than for other types of nursing and the demand for someone to do anesthesia was great. Confronted with this problem, many hospitals formed their own department and regarded the administration of anesthesia as a hospital service instead of a professional one. This resulted in many physicians losing their interest in anesthesia, particularly those who had spent but a part of their time and interest in the field. In larger hospitals and medical centers physicians stopped administering anesthesia unless they wished to continue as full time specialists. Some physicians accepted this system, working for a salary and doing contract practice of medicine. In some hospitals where physicians capable of administering anesthesia were available, it was not included as a hospital service but the anesthetist worked on a fee basis. Even at the end of the first quarter of the century very few medical schools had proper teaching facilities in anesthesia for students. Medical students from most schools saw anesthesia administered by nurses and had their practical training, if any, from nurses. It is little wonder that very few thought of choosing such a field for their life's work. Fortunately, some students encountered professional anesthetists and became interested in the specialty. In this period most surgeons' experience with physicians administering anesthesia was with those who had no schooling in the subject, and whose skill, in many instances, was limited. A fair number of physicians had become very proficient in using some anesthetic drugs and there was a small number who spent nearly all their time administering anesthesia and could rightly be classed as specialists. An organized system of teaching and dissemination of information was generally lacking. Therein lay the weakness of the specialty. What good to have so much knowledge and facts which were known but used by so few? The importance of anesthesia was recognized by some but many seemed to think these new features could be carried on readily by non-medical personnel. The specialty was not sufficiently supported financially or professionally to attract enough physicians to its fold. The only good feature about this was that very few entered the specialty who were not interested enthusiasts, whose influence was to be felt in the next period.

Though our leaders and teachers are not entirely satisfied, they have accomplished a very good job during the period from 1925 to 1948. One measure of professional activity of a group is its organizations and publications. The activity of organizations to improve anesthesia has been continued and increased during this period. Such organizations are common to all specialties as are the resulting meetings and publications for the specialty and the profession.

The New York Society of Anesthetists, organized in 1912, became the American Society of Anesthetists in 1935. With a recognized national organization, steps were taken to obtain an American Certifying Board. This was accomplished in 1937 through the cooperation of the American Board of Surgery, which permitted Anesthesiology to be affiliated with the surgical board; in 1941 this was changed so that anesthesiology had a separate board. In 1947, steps were taken to make each State Society of Anesthesiologists a component of the American Society of Anesthesiologists with a new system of representation from the en-

tire country and Canada. Canadian anesthesiologists have always carried on a welcome and active part in the organizations and progress of anesthesia of the United States. Paul Wood deserves credit as the leader, adviser and worker in the organization of anesthesiology during this era. A tribute has been paid him by Waters[68] in his discussion of progress during this time.

The most important progress in anesthesia during the last quarter century has been the improvement in teaching methods with the results of a marked increase in the number of qualified medical anesthetists. Residencies and fellowships were offered for one to three years in institutions where qualified teachers, in both theory and clinical anesthesia, had departments of anesthesia. At first, most of these were sub-sections of surgery. Before this time, the apprenticeship system had been used and a few very short courses—one to two weeks—were offered in some centers. Attendance at meetings and reading of publications, plus one's ability to learn things by oneself, determined the degree of perfection attained. The new idea of teaching anesthesia on a scientific basis, with experience under careful supervision, as during a residency, was a sound one. At the present time nearly every medical school has a teaching department in anesthesiology, as do many of the larger clinics. A teaching institution can readily get "today's work" done entirely with properly supervised students, interns and residents, with a proper teaching staff.

At the present time there is discussion regarding whether or not nurses should administer anesthesia and most of this is based on a misunderstanding of the principles involved as well as a fear of dictation by groups interested in anesthesia. Actually the nurse who administers an anesthetic is presumed to act under the guidance of a doctor of medicine, usually a surgeon. Since the nurse is an agent of the surgeon in such instances, it is the surgeon who is responsible for the acts of the nurse anesthetist. The lay superintendent of a hospital cannot assume this responsibility any more than he can assume the responsibility for the operative procedure. Unfortunately, at the present time there are not sufficient medically trained individuals who are interested and trained in anesthesia to provide the personnel necessary to carry on the present day to day work. Accordingly, it is necessary that technicians be employed as they have been in the past in those communities and institutions for which qualified anesthesiologists are not available. This does not mean that anesthesia in such institutions will not be so good as in the past, but rather that it will not progress as it should in the future. In many communities nurse anesthetists have fulfilled the obvious needs for anesthesia required by many surgeons and will likely continue to do so.

The responsibility for the administration of anesthesia is not to be lightly considered. He who administers a drug to produce surgical anesthesia, administers the most potent depressant drugs to the most extreme degree of anyone practicing medicine. Instead of hours or days to note the effects of drugs, as in many phases of medicine, the effect will and must occur in minutes or seconds in surgical anesthesia. The extreme degree of depression produced cannot be safely done with a fixed dosage of any drug. Each must be administered as required by each patient for the desired effect when that can be accomplished without endangering the patient's life. This makes it nearly impossible to order the proper dose beforehand; all of which means that the administrator must have ability to vary the dosage and other factors for each patient and each type of operation. To this must be added knowledge and understanding of pre-existing

diseases and abnormal physiology in many patients that need surgical treatment. The results produced in the disturbance of physiology of respiration and circulation during anesthesia are very unpredictable, much more so than the results from an average operation. Difficulties frequently arise which require immediate recognition, diagnosis and correction to avoid delayed or immediate damage to the patient. This can be done by the anesthesiologist without interference with the surgeon's work or peace of mind. One finds the best of surgeons very grateful for this relief from responsibility even though they were able to get along before quite well by supervising the anesthesia carefully themselves. Then comes the situation of learning when mistakes are made; a professional anesthetist may make mistakes, but, if properly trained, he will learn not to repeat them. During his training period anesthesia will not be perfect but, properly supervised, it will be safe. Non-medical personnel are apt to repeat the same mistakes more frequently unless they have proper supervision.

The problem of teaching anesthesia to graduate and undergraduate students is a serious responsibility of medically trained individuals interested and trained in anesthesia. Technicians who are unfamiliar with physiology and pharmacology, as well as the responses of the individual to disease entities can do little in the way of supplying instruction to medically trained personnel. It is not likely that students will respect the individual who is not medically trained so far as medical subjects are concerned, and this includes anesthesia. Even in the case of anesthesia programs where there is a mixture of medically trained anesthesiologists and technicians, difficulties are present in relation to training of the anesthesiologist. The facilities of well organized departments of anesthesiology are taxed to the limit with the important job of training qualified doctors of medicine and this, along with providing good anesthesia and contributing to the advancement of the field, is an important task. All communities are not of sufficient size to support an anesthetist who devotes full time to the subject. Such is likewise true in the case of other specialties. This problem has not been settled by the utilizing of technicians to carry out procedures in surgery or obstetrics. Trained anesthesiologists in smaller communities may carry on other types of practice as is common in the case of other specialties. Since it is now possible in most communities to practice anesthesiology on the same basis as consultants in other specialties, encouragement has been afforded to doctors of medicine to enter the field. The concept that the anesthesia consultant ought to have the same status as other consultants is reasonable and proper. Institutions which employ all others on the professional staff are the only ones which logically might expect to do so with the anesthesiologist.

In summary, anesthesia made little progress during the first period (1846-1900), but since 1900 there has been steady advance not only in the use of new agents and methods, but also in the matter of development of individuals highly skilled in the knowledge and technics of anesthesia. The specialties of anesthesia and surgery are closely allied. To be most effective the anesthesiologist and the surgeon must cooperate not only for the best interest of the patient but also for the advancement of both fields. Better anesthesia has permitted surgical procedures which would otherwise not be possible. The requirements of the surgeon for better anesthesia to extend his usefulness has been largely responsible for the increased demand for professional anesthetists and other advances in anesthesiology.

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THE OCULAR CHANGES ASSOCIATED WITH PHEOCHROMOCYTOMAS

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ONE of the curable types of vascular hypertension is that associated with the release of pressor substances into the blood in excess amounts by the tumors of chromaffin tissue called "pheochromocytoma", "paraganglioma", or "chromaffinoma". These tumors occur most frequently in the medulla of the adrenal gland, but they have also been found in various other locations. They can occur wherever there is chromaffin tissue in the body. Such tumors have been found in the retroperitoneal tissues, in the sympathetic ganglia along the aorta or the vena cava, in the carotid body, in the organ of Zuckerkandl at the bifurcation of the aorta, and 1 case[51] has been reported arising from the second thoracic ganglion. If the tumor is present in the adrenal medulla, it is then usually called a "pheochromocytoma", while those in other locations are designated "paraganglioma".

These adrenalin-producing tumors arise from the primitive sympathetic cells, the sympathogonia. These sympathogonia produce 2 kinds of cells in their development — the sympathetic ganglion cells and the endocrine cells. The latter are called pheochromocytes. They arise from the sympathogonia through the pheochromoblasts. The mature pheochromocytes are recognized easily in histologic preparations because of their affinity for chrome salts which stain the cellular substance brown. These cells secrete adrenalin, the pressor substance, which is then discharged into the blood stream periodically, and sometimes continuously. When they are present in abnormally large numbers, as in neoplasm, they give rise to the syndrome which has come to be recognized as indicative of the presence of a chromaffinoma.

These tumors are nearly always benign histologically, even though they may cause the death of a patient by progressive elevation of blood pressure and subsequent damage to the arteriolar system. Baumgarten and Cantor[4] have aptly stated that chromaffinomata are benign anatomically but malignant physiologically. A small number of the reported cases have actually been malignant tumors histologically which had invaded the surrounding structures.

Pheochromocytomata are relatively rare tumors. The original description of this tumor was made by Fränkel[22] in 1886 when it was found in the adrenal gland of a patient who had come to autopsy. His report included a histologic description of the pheochromocytoma as well as a clinical history, physical examination and a report of the ocular fundus. Recognition as a clinical entity stems from the report of Labbé, Tinel and Doum-

er[37] in 1922. The first surgical removal with cure of the condition was accomplished by C. H. Mayo[43] in 1926. This was a retroperitoneal tumor in the region of the kidney and pancreas and was a typical pheochromocytoma. The patient is still alive and well. The first correct preoperative diagnosis followed by cure subsequent to operation was the case reported by Pincoffs[52] and Shipley[59] in 1929 where the tumor was found in the adrenal and had grown adherent to the vena cava. In 1944, MacKeith[41] found 165 case reports. Snyder and Vick[60] in a careful review of the literature up to 1945, were able to find a total of only 84 cases which they thought were proved chromaffinomas with convincing evidence of hyperadrenalinemia. Since then about 35 additional proved cases have appeared in the literature. The most complete review of the ocular changes associated with this condition was published by Bruce[11] in 1947. He analyzed 38 case reports from the literature and discussed in detail the ocular changes in 3 cases, which also are reported elsewhere by Snyder and Vick[60] and by Goldenberg, Snyder and Aranow[24].

The so-called "adrenal-sympathetic syndrome" is the classical clinical picture in patients with pheochromocytoma. In typical cases the diagnosis is fairly simple, since there are paroxysms of hypertension associated usually with palpitation, severe headaches, extreme anxiety, severe sweating, nausea and vomiting, lacrimation and dilatation of the pupils. During such attacks there may be glycosuria, hyperglycemia, exophthalmos, swelling of the thyroid gland and the signs and symptoms of Raynaud's disease. These are all manifestations of the hypermetabolism produced by the outpouring of adrenalin into the blood. The blood pressure between attacks may or may not be elevated. It has been postulated that eventually all patients with pheochromocytoma will develop a persistent hypertension in the interim between attacks of paroxysmal hypertension. In a small percentage of patients with pheochromocytoma, the blood pressure does not become elevated in paroxysms but remains persistently at high levels and accompanying evidences of increased metabolic activity are present. Patients afflicted with pheochromocytomas are very often already under treatment and observation for diabetes, hyperthryroidism or other metabolic diseases at the time the diagnosis is made. Many of these patients have tumors of other organs of the body. About 10% of patients with pheochromocytomas have von Recklinghausen's disease.

Approximately one-third of the case reports of chromaffinomata in the literature have notes on ocular examinations. Many of these reports are brief, and only about one-half of those which include ophthalmoscopic examinations make any mention at all of the condition of the retinal vessels. From the available literature I have been able to collect reports of 66 proved cases of hypertension associated with pheochromocytoma in which examinations of the ocular fundi had been included. To these I have added 4 previously unreported cases of paroxysmal hypertension caused by pheochromocytoma proved by surgery at the Mayo Clinic. These 70 cases are considered here and the retinal lesions analyzed.

For consideration of the retinal lesions present these cases may be divided into 3 groups: 1, those with paroxysmal attacks of hypertension but with normal blood pressure between attacks; 2, those with paroxysmal attacks of hypertension but with persistent elevation of blood pressure above 150 systolic or 90 diastolic between attacks; and 3, those with a persistently elevated blood pressure which gave no history of any form of paroxysmal episodes. In each of these

3 groups there occur cases which show: A, no pathological changes in the retinas; B, only hemorrhages in the retina; C, only vascular changes without exudates; and D, retinopathy or neuroretinopathy. These data are shown in Table 1.

TABLE 1.—RELATION OF HYPERTENSION TO OCULAR CHANGES.

	Paroxysmal Hypertension	Persistent Hypertension With Paroxysms	Persistent Hypertension Without Paroxysms	No. of cases	Total %
Normal Fundi	10	4	1	15	21.4
Hemorrhages only	4	2	0	6	8.6
Vascular changes without retinopathy	8	8	2	18	25.7
Retinopathy or Neuroretinopathy	2	23	6	31	44.3
Total	24 (34.3%)	37 (52.8%)	9 (12.9%)	70	100.0

Thus, it is seen that among 24 patients with normal blood pressure between attacks of paroxysmal hypertension, 10 (41.6%) had normal fundi, while only 5 of 46 patients (10.9%) with persistent elevation of blood pressure had no lesions in the retina. Four of the latter 5 had paroxysmal episodes and 1 had no such attacks. Among the 12 patients without persistent hypertension who had retinal lesions but no retinopathy, 4[15,32,53,70a] had only minimal to moderate sclerosis of the retinal arterioles, 2[1,69] had only arteriolar narrowing, and 1[57b] had grade 1 narrowing and grade 1 sclerosis. The notation on Baker and Rienhoff's case[2] stated only that there were arterial changes and a few hemorrhages in the retina. Four other authors[38,56,62,64] had merely noted hemorrhages in the retina without observing any changes in the retinal vessels. Thus, 6 of the 24 patients who did not have constant elevation of blood pressure are said to have had sclerosis of the retinal arterioles (25%). Two patients in whom the blood pressure was not elevated between the paroxysms had retinopathy. Bensis and Codonnis' patient[6] had a long history of kidney disease with renal stones. For 8 months he had paroxysmal attacks during which the blood pressure rose from 140/70 to 290/200. The patient died of congestive heart failure, and a pheochromocytoma of the adrenal was found at autopsy. Ophthalmoscopic examination revealed papilledema and many hemorrhages and exudates; no mention was made of the condition of the retinal arterioles. Goldner's patient[25] showed about grade 1 narrowing and questionable sclerosis of the retinal arterioles, and there were many cotton wool patches and hemorrhages in the retina. There was complete return to normal after operation.

The second group of patients, those having persistent elevation of blood pressure in the interim between paroxysmal episodes, show a greatly increased incidence of retinopathy over the first group. Only 4 (10.5%) of these patients were reported as having normal ocular fundi. Hyman and Mencher's[33c] patient was reoperated by Calkins and Howard[12a] 4 years later because of persistent symptoms and another tumor was removed, with resultant complete cure. There had at no time been any change observable in the eyegrounds. Muntz, Ritchey and Gatch[47] reported a patient with paroxysmal hypertension and elevated interim blood pressure for 2 years. This patient had bilateral adrenal tumors and associated malignancy of the thyroid with metastases. This patient had only slight tortuosity of the arterioles with no sclerosis nor hemorrhages. During attacks, the authors noted scleral injection and exophthalmos. The other 2 patients[28,61a] with normal retinas were operated and cured.

Bartels and Wall[3] noted only many

small retinal hemorrhages in their diabetic patient who was 65 years old and had had paroxysmal hypertension for one year prior to his death. Washington and his collaborators[68] mention only a few recent hemorrhages at the optic disk margins in a patient who at autopsy was found to have severe necrotizing arteriolitis in many organs of the body. Of the 8 remaining patients in this group, 5 cases had about grade 1 narrowing and grade 1 sclerosis of the retinal arterioles. These were reported by Blacklock *et al.*[9c], Kvale *et al.*[36], Goldenberg, Snyder, and Aranow[24c] with description of fundi by Bruce[11]. The case reported by Beer, King and Prinzmetal[5] was also reported by Hyman and Mencher[33a] and by Calkins and Howard[12b]. The case of Engel, Mencher and Engel[17] was again reported by Hyman and Mencher[33a] and by Mencher[45]. Three cases[44,57a,58] had somewhat more marked vascular changes.

Of the 37 patients reported who had persistently elevated blood pressure between attacks of paroxysmal hypertension, 23 (62.2%) had retinopathy or neuroretinopathy. Several authors[30,31a,31c,49,66] mentioned only that albuminuric retinitis or hypertensive retinopathy was present, but they gave no detailed description of the retinal lesions. This was true also of Gortz's[26] patient reported by Espersen and Dahl-Iversen[19]. Rodin[54] published a very complete description of the ocular fundi in a patient with a pheochromocytoma successfully removed surgically. The case had been previously reported by Biskind, Meyer and Beadner[8]. Photographs of the retinas taken at intervals after surgery revealed the gradual disappearance of papilledema, hemorrhages, exudates, macular stars and narrowing of the retinal arterioles. The ocular fundi were reported as normal 3½ years after the operation. Five patients[14,21,23,24c,27] who had papilledema, hemorrhages and exudates were said to have arterioles narrowed variously from grade 1 to "extremely spastic"[21]. All recovered and had a progressive improvement in the retinal picture postoperatively.

In this group of patients, it was much more common to have neuroretinopathy than it was merely to have cotton-wool patches and vascular changes. Papilledema was stated definitely to be absent in only 3 cases: those reported by Coller *et al.*[13], Edward[16], and the case published by Snyder and Vick[60b] with detailed ocular description by Bruce[11]. In addition to the 6 patients mentioned above in which papilledema was associated with spastic constriction of the arterioles, papilledema was noted in 9 patients[20,22,18,40,48,51,55,60a,65] associated with retinal arteriolosclerosis ranging from grade 1 to grade 3 and arteriolar narrowing ranging from grade 1 to grade 3. Most authors who took note of the arterioles remarked on the high degree of spasticity in the vessels, but only Green[27] and Volhard[65] commented on the presence of localized constrictions in the arterioles. Coller and his collaborators[13] mentioned the presence of endarteritis and periarteritis. Snyder and Vick[60b] and later Bruce[11] reported an 11 year old negro girl who had one paraganglioma at the bifurcation of the aorta and another in the right epigastric area. She was noted to have pronounced narrowing and tortuosity of the arterioles, nicking of the veins and beginning macular stars but no papilledema.

Among the 37 patients with paroxysmal hypertension but with persistence of elevated blood pressure between attacks, 16 (43.2%) were said to have retinal arteriolosclerosis.

Among the 9 patients with proved pheochromocytomas in whom the blood pressure was steadily elevated and no definite paroxysms occurred, 1 (11.1%) had normal ocular fundi, 2 (22.2%) had only retinal vascular lesions and 6 (66.7%) had retinopathy.

Linder and Tyler[39] reported a patient with chronic duodenal ulcers and with hypertension but without paroxysmal episodes who complained only of headaches and dizziness for 4 years, but was found to have a pheochromocytoma on autopsy. Her retinal vessels were reported to be normal. Thorn, Hindle and Sandmeyer[63] and Binger and Craig[7] each reported a patient with persistent hypertension cured by removal of a pheochromocytoma, neither patient having had paroxysmal hypertension. Both these patients had severe arteriolar narrowing. Thorn's patient had severe sclerosis, while Binger's patient had little or no sclerosis of the retinal arterioles, but did have grade 1 local spastic constrictions in the arterioles.

In 6 patients with persistent hypertension but without paroxysmal attacks, ophthalmoscopic examination revealed the presence of retinopathy. In 2, those of Brenner *et al.*[10] and Holst[31b], the descriptions of the ocular fundi were rather brief. Brenner noted papilledema, narrowing of the arterioles, macular stars and numerous hemorrhages. Holst mentioned only poor vision and albuminuric retinitis in a 19 year old male with considerable fluctuations in blood pressure but no paroxysmal attacks. Kremer[35] mentions nephritic retinitis with arteriolosclerosis and bilateral optic atrophy in his patient. One of Snyder and Vick's[60c] patients, also reported by Goldenberg, Snyder and Aranow[24a] and by Bruce[11], was a 12 year old girl who had no paroxysmal hypertension nor great fluctuations in blood pressure, which remained about 180-240 systolic and 120-170 diastolic. Her presenting complaint was excessive perspiration. Her eyes were at first normal, but she gradually developed papilledema, arterial spasm, venous compression, hemorrhages, exudates, and diminution of visual acuity coincident with the development of macular stars. Six months after her 2 adrenal pheochromocytomas were removed, she had no papilledema, hemorrhages or exudates and the blood pressure was normal. Edward[16] noted hemorrhages, exudates, and irregular constrictions in the arterioles in a patient with pheochromocytoma who had had no symptoms prior to the sudden onset of hemiplegia. This patient died 7 days after this incident. His blood pressure remained constantly at 220-230/140 during this period.

A 21 year old girl was seen at the Mayo Clinic with a 3 year history of persistently elevated blood pressure, nervousness, severe sweating, marked intolerance to heat, and an elevated basal metabolic rate. She was discovered to have a pheochromocytoma of the right adrenal as well as a grade 2 carcinoma of the pancreas. Her eyegrounds showed papilledema, grade 2-3 narrowing, minimal sclerosis, and grade 2 focal constrictions in the arterioles. There were numerous cotton wool patches, hemorrhages and partial macular stars in both eyes. Postoperatively, there was a gradual regression of all retinal changes. At the present time, 1½ years following operation, her blood pressure is normal, she notes only mild heat intolerance, her basal metabolic rate is at the upper limits of normal and she has only about grade 1 narrowing of the retinal arterioles with complete disappearance of neuroretinopathy.

In this small group of 9 patients with constant hypertension, 5 (55.5%) were said to have retinal arteriolosclerosis.

Several authors observed the eyegrounds during the paroxysmal attacks of hypertension in their patients and reached varying conclusions. The patient reported by Kvale, Roth, *et al.*[36] was observed by Dr. H. P. Wagener during an attack. He could detect no change in the calibre or appearance of the retinal vessels. The same was

true in the patient reported by C. H. Mayo[43]. Hyman and Mencher[33b] and Evans[20] noted slightly increased narrowing and propulsive pulsation of the arterioles during an attack. Snyder and Vick's patient [60a] was examined during an attack in which the diastolic pressure was measured at 300 mm. of mercury. The pupils were then widely dilated, the papilledema increased, and the arterioles further constricted and there was increase also in hemorrhage, exudation and arteriovenous nicking. Lecuire *et al.*[38] reported that both the arteries and the veins in the retina dilated and the diastolic blood pressure in the central artery of the retina rose from 45 to 70 in their patient during an attack. Perera[50] noted that during attacks his patient showed very definite spasm of the arterioles, with considerable narrowing and irregularity.

Most authors report wide dilatation of the pupils and increased lacrimation during attacks of paroxysmal hypertension. Several[47,62,69] noted exophthalmos coincident with great increase in blood pressure. Philips[51] described a left-sided Horner's syndrome in the patient he reported who had a paraganglioma in the vicinity of the first left thoracic ganglion. He ascribed the Horner's syndrome to involvement of the efferent sympathetic fibers passing through the first thoracic ganglion from the spinal cord on their way to the cervical sympathetic chain.

Whether the elevation of blood pressure, originally paroxysmal in type, resulting from a pheochromocytoma, will become constant eventually in all cases is still a matter for conjecture. In this series there are 5 patients[34,38,56,61b,62] who had had paroxysms of hypertension for from 5 to 10 years. They each still had normal blood pressure between attacks when examined, and there was no retinopathy. And yet, if it is assumed that those patients who do have persistent hypertension have a superimposed essential hypertension, the blood pressure should not return to normal after removal of the pheochromocytoma. Postoperative blood pressures are recorded in 25 of these patients. Among them the blood pressure remained slightly elevated in 6 (24%)[7,8,13,14,25,28], in 5 of whom retinal arteriolosclerosis was present. The fact that retinal arteriolosclerosis was stated to be present in a fair percentage (38.6%) of these patients, would seem to indicate that elevation of blood pressure in itself, from whatever cause, can produce the ophthalmoscopic appearance, at least, of retinal arteriolosclerosis. It seems fairly well established that retinopathy and neuroretinopathy do not usually develop in patients with pheochromocytoma until the blood pressure becomes persistently elevated between attacks. However, it is evident from this series that the severe retinal changes can occur occasionally even with normal interim blood pressures[6,25]. It is of interest that 10 of the 70 cases occured in children under the age of 16. In all of them, retinopathy was present.

As has been noted before by Bruce[11] and Wagener[67], the retinopathy associated with the hypertension of pheochromocytoma is indistinguishable ophthalmoscopically from that of primary (essential) hypertension, although, as in the matter of arteriolosclerosis itself, the data is not too accurate or conclusive. It is of interest that among the 31 cases of retinopathy, 19 (61.4%) would seem to be of the acute hypertensive type without sclerosis of the arterioles.

A further matter of interest may be noted. In 5 cases[8,24a,25,63,70d], there was reported a diminution in the degree of arteriolosclerosis of the retinal arterioles postoperatively. This would seem to indicate that in severe degrees of hypertension with severe narrowing of the retinal arterioles, there may be a heightened arteriolar light reflex which

simulates the higher degrees of sclerosis. This phenomenon would tend to be a misleading factor in assessing and interpreting vascular damage.

Since the ophthalmologist sees many of these patients primarily because of visual difficulties, he should bear in mind the possibility of the presence of this curable disease when confronted with hypertensive retinopathy, especially if the retinopathy is of the acute hypertensive type without associated retinal arteriolosclerosis, and perhaps especially if it is seen in a child. The further point is brought out by a review of these cases that retinopathy with papilledema even in the presence of retinal arteriolosclerosis is not necessarily a fatal prognostic sign. The diagnosis of terminal malignant hypertension should not be considered as established until all possible causes of secondary hypertension have been ruled out.

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PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
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Studies on the Action of a Synthetic Heparinoid*. JOSEPH SEIFTER, M. D., and ALBERT J. BEGANY, A.B. (Wyeth Institute of Applied Biochemistry, Phila.).

THE synthetic antithrombins available heretofore are too toxic for clinical use. However, Snyder and Alburn have recently prepared Hepinoid, a polysulfuric ester of polyanhydromannuronic acid, which does not appear to have this drawback. The pharmacology and toxicology of Hepinoid have been investigated in animals and humans and were found closely to resemble those of heparin. In the study briefly reported here, attention has been centered on elucidating the causes for the relatively rapid dissipation *in vivo* of a single therapeutic dose of heparin or Hepinoid.

The toxicity of Hepinoid was found to be no greater than that of heparin, and about 1/10 to 1/20 that of other heparinoids. This can be seen from the following list of LD_{50} values determined as mg./kg. of mouse by intravenous injection: heparin, 1500-2000; Hepinoid, 1898; cellulose sulfuric ester, 100; oxycellulose sulfuric ester, 200.

The anticoagulant potency of therapeutic doses of Hepinoid in humans is 1/7 that of heparin. In all species tested, both the intensity and the duration of action are proportional to the dose administered. However, when relatively large doses are administered, such as 1/10 the LD_{50}, the potency of both anticoagulants are practically identical and the duration of action is prolonged for 10 to 11 hours.

The relatively brief duration of action of heparin has been variously attributed to urinary excretion, phagocytosis by the reticulo-endothelial cells, destruction by the enzyme heparinase, and inactivation by thromboplastic substances in the tissues. Experiments were made, therefore, to determine whether Hepinoid was inactivated by any of these mechanisms and also to determine how valid these are for heparin.

Following intravenous injections of therapeutic doses of heparin or Hepinoid it was never possible to recover more than 30% in the urine. It appeared, therefore, that excretion of these substances in the urine is not the important factor in the dissipation of their action. This was conclusively confirmed when bilateral nephrectomy failed to prolong the anticoagulant effects of a therapeutic dose of either substance.

Nor was the duration of anticoagulation significantly affected by any of the following procedures: splenectomy; complete hepatectomy; combined nephrectomy, splenectomy, and hepatectomy; injections into the bone marrow of the tibia; ligation of the carotid and vertebral arteries; blockade of the reticulo-endothelial system with India ink—to the point where frequently an endogenous anticoagulant is released; stimulation of the reticulo-endothelial system by histamine, and depression of it by antihistaminic drugs. All of these negative results exclude the following as being responsible for the relatively brief effect of a therapeutic dose of heparin or Hepinoid: urinary excretion,

* The term heparinoid is introduced to include all the synthetic antithrombins, in order to distinguish them from the naturally occurring heparin.

as already mentioned; enzymatic destruction in the liver; inactivation by thromboplastic substances in certain tissues; and phagocytosis by cells of the reticulo-endothelial system. Phagocytosis was seen in intact animals, but was most active after the anticoagulant effect had worn off.

Heparin and Hepinoid appear, therefore, to be inactivated in the peripheral blood stream, and indeed the results of current *in vitro* experiments tend in this direction. The inactivating agent appears to be an antithrombin inhibitor.

Glycolysis in Homogenates and Extracts of Malignant Tumor. Otto Meyerhof, M. D., and Jean R. Wilson, M. S. (Dept. of Physiological Chemistry, Univ. of Penna.).

In homogenates and centrifugal extracts of malignant tumor a steady glycolysis of free sugar of a rate 2 to 3 times that of tissue slices is obtained if the activities of the hexokinase and the ATPase are brought into step. This is made possible either by addition of purified hexokinase from yeast or without any foreign enzyme if the tumor ATPase is specifically inhibited.

ATPase of tumor is weakened by several days' freezing but with still greater regularity by narcotic or specific inhibition. Most effective are very high members of narcotic series; octyl-, decyl-, and dodecylalcohol and toluene are suited best. A similar effect is obtained with about M/100 of Na azide. Most work was done with octyl alcohol. The strong inhibition of the ATPase of tumor by higher members of the narcotic series is remarkable because the ATPase of normal tissues is only slightly affected, sometimes in the direction of inhibition, sometimes in the direction of activation.

With octylalcohol Q_{La} values of homogenates of 50-60 are easily obtained and somewhat smaller (40 - 45) for extracts. The differences in the turnover rates for various sugars, especially for glucose and fructose closely resemble those of the living tumor tissue in the absence of inhibitors.

Further Studies of the Effect of Hypertonic Glucose on the Circulation. James P. Walsh, M. D. (Dept. of Therapeutic Research and of Medicine, Univ. of Penna.).

The initial studies (unreported) by Dr. Marcel Segers and the author had demonstrated that after the rapid intravenous injection of 50 cc. of 50% glucose in 14 subjects with cardiac disease, there was a prolonged increase in cardiac output as measured by the ballistocardiograph. In contrast, in 9 subjects with normal hearts, although the cardiac output increased initially, it returned to the basal level in 6 to 8 minutes. There was little or no change in blood pressure or cardiac rate after the glucose injection in either normal or cardiac patients.

Further studies after similar injections of glucose included the measurement of peripheral venous pressure by a saline manometer in 2 normal subjects and 4 with heart disease; and of plasma volume by the dye T-1824 in 4 normal subjects and 10 with heart disease. These determinations and estimates of cardiac output by the ballistocardiograph were made at intervals of 5 to 15 minutes for 30 to 45 minutes after the glucose injection.

There was a small initial increase in peripheral venous pressure after glucose injection with a prompt return to the basal level. In 45 paired estimations of cardiac output and plasma volume, there was a statistically significant correlation between the changes occurring in each after the injection (correlation coefficient 0.41). However, this correlation was not a close one and change in plasma volume was by no means always followed by a concomitant charge in cardiac output.

Since the change in blood volume affects venous pressure so little, it probably does not cause the prolonged increase in cardiac output; so there

may well be a specific stimulating effect of glucose on the failing myocardium as has been observed in the animal heart-lung preparation.

Further Studies on Intraarterial Temperature. LEON EISENBERG, M. D., and H. C. BAZETT, M. D. (Dept. Physiol., Univ. of Penna.)

PREVIOUS reports have given evidence of considerable exchange of heat between cool blood returning in venae comites from the periphery of limbs and warm blood flowing out of adjacent arteries. Thereby venous blood is rewarmed at the expense of arterial cooling, even to temperatures below 22° in the radial artery. The existence of such exchanges may be demonstrated readily in animals by perfusing a femoral vein with cooled saline. A steep thermal gradient may thus be set up within a short length of femoral artery, which varies with the rates of flow in both artery and vein.

General reflexly-induced vascular responses to warmth are discussed in the literature without regard to the complexities introduced by vasodilation and these thermal exchanges, which can account for the long delay in observed effects. Exposure of the hands to hot water may induce a rise in temperature in the dorsalis pedis within one minute but this can be counteracted by a simultaneous fall in temperature in central vessels. Increased blood flow raises thermal conductance, redistributing heat and warming the colder peripheral areas at the expense of those that are warmer and more central. Vasodilation causes not only greater inflow of blood but also more rapid return of cooled venous blood. Even in an artery as peripheral as the radial these effects can for some time compete with one another, delaying a rise of temperature or even producing an initial fall as the result of vasodilation.

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BOOK REVIEWS AND NOTICES

HISTORY OF MEDICINE. By CECILIA C. METTLER, PH.D., late Asst. Prof. of Medical History, Univ. of Georgia. Pp. 1215; 16 ills. Phila.: Blakiston, 1947. Price, $8.50

FORTUNATELY the manuscript of this latest addition to systematic works on medical history, which we are told was under preparation for somewhat over 9 years, was completed shortly before the untimely death of its talented authoress. For it is a valuable contribution, both in the utility of its novel approach, in the general accuracy of its considerable factual content, and in the very liberal use of quotations from the writings of the great figures of the past. These, easily picked out in small type, range from 5 or 6 lines to 2 or more pages in length and probably constitute an eighth or more of the text. Thus in the 40 pages devoted to Pathology and Bacteriology, there are over 30 such excerpts.

As a zealous but honest professional teacher of medical history, Dr. Mettler appreciated the comparative failure of its teaching to medical students in this country. This and her belief in the value of medical history in aiding the study of medicine, as opposed to its "dubious cultural value", has largely determined the general form of the book. To aid in teaching the subject "on a correlative basis", the Contents are arranged under 15 main topics, corresponding in general to those of the average medical curriculum. Each of these is subdivided, mostly chronologically but also at times geographically or by special subjects, such as Morbus Gallicus. The Twentieth Century, already among the greatest in medical achievement, has not been included. Therefore, if the history of such classical discoveries as insulin, liver extract, the virus diseases and the rest that crowd in increasing measure each decade of the century is to be correlated with the curriculum, it must be without the help of this book.

The book will, to be sure, be useful in giving the medical student "an introduction to the principles underlying the development of the fields" of his curriculum, and in providing some familiarity with "the climate of opinion" surrounding a given advance or period. But when it is also aimed "to meet the particular needs of the specialist who is interested in a single field", this simply can't be done properly, any more than it can in any other one volume history of such a vast subject. To be sure, the seeker is aided by copious reference notations—every column contains one or more references to individual authors or incidents—and in addition at the end of every chapter are found several pages of selected readings covering various subdivisions of the chapter.

How will this attractive book be of use and earn the success that it deserves? As supplementary to an inspiring teacher, the student being given adequate time, it should correlate the subject more easily than other works of its kind. There will be some medical history readers who will get from it the entertainment and scholarly or recondite background sought by the author, and this frequently reinforced by the original writer's own words. A good index, too, increases its value as a book of reference. The unusual arrangement of chapters of course will tend to hinder progressive reading, but who reads such books as simple narratives anyhow?

The book, then, may be said to occupy a middle position between the conventional Histories and such a series as Clio Medica (taking the series as a whole), with a dash on the side of such anthologies as Classical Descriptions of Disease. It will be a welcome addition to the medical history shelf. E. K.

RESEARCHES ON NORMAL AND DEFECTIVE COLOUR VISION. By W. D. WRIGHT, A.R.C.S., D.Sc. Technical Optics Section, Imperial College of Science and Technology, London. Pp. 383; 233 ills. St. Louis: C. V. Mosby, 1947. Price, $10.00.

THE first 2 chapters in this book serve as an introduction to the eye as a sense organ. In this section, the physiology of the retina is briefly reviewed in the light of recent knowledge. The rest of the book is largely composed of data on color vision obtained by the author's own researches. He is well known in this field and those who are interested in color vision will find much data of value. The book is not recommended for those who have not had laboratory experience in this field. F. A.

DYNAMIC ASPECTS OF BIOCHEMISTRY. By ERNEST BALDWIN, B.A., Ph.D., University Lecturer in Biochemistry, formerly Fellow of St. John's College, Cambridge. Pp. 457; 33 figs. New York: Macmillan, 1947. Price, $4.00.

THE vital aspects of 2 leading fields in biochemistry—enzymes and metabolism—are rather thoroughly considered in the light of past and new developments. The book is written from an investigator's viewpoint and is not a mere collection of facts. Historical development of different phases are included, which makes for easier understanding. Experiments are often described in considerable detail, and experimental methods are criticized in unbiased fashion. The text runs the gamut of enzyme systems and includes the new concepts of high energy exchange in ATP metabolism. Fat, protein, and carbohydrate metabolism is thoroughly discussed and illustrated with ample formulae. There is an interesting chapter on comparative aspects of nitrogen excretion. Where gaps in knowledge exist, speculation is often resorted to, but the author usually indicates clearly the speculative phases. I. Z.

MEDICINE. (Volume I) THE PATIENT AND HIS DISEASE. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge; Physician to the London Hospital and Dean of the Medical School. Pp. 383. Baltimore: Williams & Wilkins, 1947. Price, $6.00.

THIS book is another brave attempt to achieve the impossible; "it is intended to inculcate an attitude of mind. It is written to present facts which could be deduced from principles being committed to memory unnecessarily". This highly desirable goal is unfortunately not reached by this volume.

Chapter I in 38 pages discusses "Energy and matter—Life—Organic evolution—Heredity—Development – Constitution – Consciousness and mind." At this rate it is easy to see how much can be crowded into the remaining 341 pages. Actually, an enormous number of flat statements are made and there is a disappointing lack of the integration which the author hoped to present.

In the hurried attempt to cover everything, it is inevitable that dogmatic unqualified statements are made. Many of these are misleading to a student. One, on page 153, is inexcusable "A rectal examination, easy under hospital discipline and routine, more difficult under other circumstances, is necessary in adult patients with diarrhoea, rectal bleeding, or prostatic symptoms and in every obscure or difficult case." Shades of Sir William Osler! A rectal examination is an integral part of the routine examination of every patient. O. P.

THE BIOLOGY OF MELANOMAS. Edited by ROY WALDO MINER, MYRON GORDON, and LOTHAR SALIN. Vol. Pp. 478; 107 plates. New York: The New York Academy of Sciences, 1948. Price, $5.00. (To members, $4.00.)

The experiments and interpretations collected in this volume do much to clarify the poorly understood subjects of pigment biology and pigmented tumors. Each chapter is written by a different group of authors, and the approaches to the subject vary widely. The aspects considered range from genetics of pigmentation to the chemistry of melanin. Many papers deal with pigmentation of the lower animals, and in relatively few chapters are specifically human aspects considered. Of particular interest are the chapters written by Masson, by Becker, and by Du Shane on pigment cells in man and in the vertebrates. All papers on morphologic subjects are followed by excellent black and white illustrative photographs. A. R.

PUBLIC HEALTH ADMINISTRATION IN THE UNITED STATES. By WILSON G. SMILLIE, M.D., Prof. of Public Health and Preventive Medicine, Cornell Univ. Medical College, 3rd ed. Pp. 637; 43 ills. New York: Macmillan, 1947. Price, $6.50.

THIS edition, like its predecessors, is aimed to elicit the interest of the practicing physician in disease prevention and control. The text is so clear and each subject is discussed so completely and satisfactorily, that the author's aim has obviously been achieved. The volume is a superior textbook for students and an indispensable reference work and guide for health officers.

Here we find, in their proper places, all the great developments from research, speeded up so productively during World War II and since, which are transforming our concepts of disease control in many fields.

The final chapter discusses with great wisdom the development and the details of "The National Health Program." This reviewer is not acquainted with a more clarifying exposition of this matter which has been the subject of so much controversy. A. H.

NEW BOOKS

Modern Trends in Dermatology. Edited by R. M. B. MacKenna, M.A., M.D. (Camb.), F.R.C.P. (Lond.), Lecturer in Dermatology, St. Bartholomew's Hospital, London. Pp. 432; 32 ills. New York: Paul B. Hoeber, 1948. Price, $8.50.

Physical Treatment of Injuries of the Brain and Allied Nervous Disorders. By K. M. Hern, M.C.S.P., Diploma of Liverpool Physical Training College. Pp. 96; 34 ills. Balt.: Williams & Wilkins, 1947. Price, $4.00.

Glomerular Nephritis. By Thomas Addis, M.D., F.R.C.P. (Edin.). Pp. 338; 56 figs. New York: Macmillan, 1948. Price, $8.00.

Biology of Disease. By Eli Moschcowitz, M.D., Mt. Sinai Hospital Monograph No. 1. Pp. 221. New York: Grune & Stratton, 1948. Price, $4.50.

Pediatrics for Nurses. By Arthur G. Watkins, M.D., F.R.C.P., Lecturer Welsh National School of Medicine. Pp. 192; 22 ills. Balt.: Williams & Wilkins, 1948. Price, $3.50.

Feeding Problems in Man as Related to Environment. An Analysis of U. S. and Canadian Army Ration Trials and Surveys, 1941-1946. By Robert E. Johnson, M.D., and Robert M. Kark, M.R.C.P. (Lond.). Pp. 94; 13 figs. Chicago: Quartermaster Food and Container Inst. for the Armed Forces, 1948.

The 1947 Year Book of Pathology and Clinical Pathology. Edited by Howard T. Karsner, Prof. of Pathology, Western Reserve Univ., Herbert Z. Lund, M.D., and Arthur Hawley Sanford, M.D., Prof. of Clinical Pathology, Univ. of Minnesota. Pp. 558; 102 ills. Chicago: Year Book Publishers, 1948. Price, $3.75.

Voluntary Medical Care Insurance in the United States. By Franz Goldmann, M.D. Pp. 228. New York: Columbia Univ. Press, 1948. Price, $3.00.

"A companion volume to *Public Medical Care* by the same author . . . . It traces the progress of major types of programs from the mid-19th century to the present . . summarizes the limitations and possibilities of the entire principle of voluntary medical care insurance."

Chronic Ill-Health. By Rosa Ford, M.B. (Lond.), D.O. (Oxon.), Late Ophthalmic Surgeon, South London Hospital for Women. Pp. 104; 13 ills. London: Henry Kimpton, 1948. Price, $3.00

What Is Psychoanalysis? By Ernest Jones, M.D. Pp. 126. New York: International Universities Press, 1948. Price, $2.00.

Akute Aussere Prozesse die Physiologie, der Chirurgischen und Konservativen Therapie. von Dr. Josef Riese, Privatdozent für Chirurgie, Universitat Wien. Pp. 326. Wien: Wilhelm Maudrich, 1948. No price given.

Klinisch-Praktische Bewertung des Elektrokardiogramm-Befundes. von Dr. Oskar v. Zimmermann-Meinzingen. Pp. 227; 136 ills. Wien: Wilhelm Maudrich, 1948. No price given.

Projective Methods. By Lawrence K. Frank, Director, Zachry Institute of Human Development, New York. Pp. 86. Springfield, Ill.: Charles C. Thomas, 1948. Price, $2.75

The author describes the tendency in all science nowadays to study process rather than structure, and goes on to show that projective tests are trying to give initial understandings of both the general process of personality development and the special processes of the individual person, with no interest in statistically established norms. There is an excellent bibliography of 18 pages.

The reader will find this book a short evaluation of projective methods against the large background of psychology and science. E. B.

The Clinical Picture of Thyrotoxicosis. By Peter McEwan, M.A., M.B., Ch.B., F.R.C.S. (Edin.). Pp. 127; 4 ills. Edinburgh and London: Oliver and Boyd, 1948. Price, 15/ net.

This small book presents the clinical symptoms of thyrotoxicosis in a simple, readable fashion. There is little attempt made to explain the pathologic physiology underlying them and none to discuss organic changes which present few symptoms, as for example, lesions in the liver. The mortality figures and geographic distribution of the disease that are given are for England.

The reviewer does not recommend the book for the specialist and doubts its usefulness to the average general practitioner, although certain symptoms are discussed which are not commonly thought of as important in thyroid disease

I. R.

Pathology of Tumours. By R. A. Willis, D.Sc., M.D., F.R.C.P., Sir William H. Collins, Prof. of Human and Comparative Pathology, Royal College of Surgeons, London. Pp. 1050; 500 ills. St. Louis: C. V. Mosby, 1948. Price, $20.00.

Rheumatism and Soft Tissue Injuries. By James Cyriax, M.D., B.Ch. (Cantab.), Physician-in-Charge, Physiotherapy Dept., St. Thomas's Hospital, London. Pp. 410; 107 ills. New York: Paul B. Hoeber, 1947. Price, $9.50.

Fundamentals of Human Reproduction. By Edith L. Potter, M.D., Assoc. Prof. of Pathology, Department of Obstetrics and Gynecology, Univ. of Chicago. Pp. 231; 92 figs. New York: McGraw-Hill, 1948. Price, $3.50.

Written for nurses, its clear simplification may also be useful to medical students.

Progress in Clinical Medicine. Edited by RAYMOND DALEY, M.A., M.D. Camb., M.R.C.P., and HENRY G. MILLER, M.D. Durh., M.R.C.P., D.P.M. Pp. 356; 22 figs., 15 plates. New York: Grune & Stratton, 1948. Price, $6.00.

Twelve British physicians present some of the important developments of the past few years.

Topics in Physical Chemistry. By WILLIAM MANSFIELD CLARK, Ph.D., Sc.D., DeLamar Prof. of Physiological Chemistry, Johns Hopkins Univ. Pp. 738. Balt.: Williams & Wilkins, 1948. Price, $10.00

AS THE title implies, this book is not a text on physical chemistry, nor is it to be taken as a complete reference book. It is rather a series of stimulating dissertations on various aspects of physical chemistry—such as gas laws, thermodynamics, diffusion, semipermeable membranes, mass-action laws, oxidation-reduction systems and a host of other related and unrelated topics. Numerous techniques are described and special attention is given to possible sources of error. In some sections there is a lack of continuity in the text. Much useful information, as well as thought-provoking treatment of many subjects, makes it valuable to scientists in most fields. I. Z.

Man - Weather - Sun. By WILLIAM F. PETERSEN, M.D. Pp. 462; 294 figs. Springfield, Ill.: Charles C Thomas, 1948. Price, $10.00.

THIS is a further presentation by Dr. Petersen of his studies and speculations on the interrelation of the human organism and its inorganic evironment, leading to the concept of "man as a cosmic resonator." One of its more interesting features is a detailed six weeks' day-by-day study of adult triplets, extending over 100 pages.

The Back and Its Disorders. By PHILIP LEWIN, M.D., F.A.C.S., Prof. of Bone and Joint Surgery, Northwestern Univ. Medical School. Pp. 157; 15 ills. New York: McGraw-Hill, 1948. Price, $2.50.

THIS book is intended as a guide for the layman, briefly describing conditions and mechanisms causing backache. It is not a diagnostic guide. The author has attempted to give laymen a description of the anatomy and physiology of the back. The difficulties of diagnosis and treatment are stressed.

P. C.

NEW EDITIONS

Endotracheal Anesthesia. By NOEL A. GILLESPIE, M.A. (Oxon.), M.D. (Wis.), Assoc. Prof. of Anaesthesia, Univ. of Wisconsin. 2nd ed. Pp. 237; 56 figs.; 1 color plate. Madison: University of Wisconsin Press, 1948. Price, $4.00.

THIS edition represents the revision and enlargement of a work which, even without such improvements, was outstanding. Fifty pages have been added. The advances in endotracheal anesthesia during the past 5 years have been summarized. The only criticism the reviewer has is of the quality of paper and the print. The first edition was preferable from these standpoints. R. D.

Diseases of the Nose, Throat and Ear. By I. SIMSON HALL, M.B., Ch.B., Surgeon to the Royal Infirmary, Edinburgh. 4th ed. Pp. 463; 34 ills., 8 color plates. Balt.: Williams & Wilkins, 1948. Price, $4.50.

THIS well-illustrated concise and elementary text-book has been brought up to date by including such topics as the fenestration operation and penicillin. Designed for the busy practitioner and the student, it serves as a brief introduction to otolaryngology but is too superficial to serve as a reference work. H. S.

Stethoscopic Heart Records. By GEORGE D. GECKELER, M.D., Assoc. Prof. of Medicine, Hahnemann Medical College. Revised edition. New York: Columbia Records, Inc. Set M-735. No price given.

FOUR 12 inch records, with a printed statement on the inside of the cover about their purpose and use.

Bergey's Manual of Determinative Bacteriology. Edited by ROBERT S. BREED, New York State Experiment Station, Cornell Univ., E.G.D. MURRAY, McGill Univ., and A. PARKER HITCHENS, Univ. of Pennsylvania. 6th ed. Pp. 1529. Balt.: Williams & Wilkins, 1948. Price, $15.00.

THE present edition of Bergey's well-known manual is a complete revision of the 1939 volume. It has been reset in double column format and the amount of material included has been greatly increased. Almost 300 additional species are described. The viruses and rickettsiae are included for the first time. An extensive Source and Habitat index is also new.

This authoritative reference work will continue to be indispensable in all laboratories of bacteriology. C. B.

An Introduction to Physical Methods of Treatment in Psychiatry. By WILLIAM SARGANT, M.A., M.B. (Cantab.), Hon. Psychiatrist, West End Hospital for Nervous Diseases, London, and ELIOT SLATER, M.A., M.D. (Cantab.). 2d ed. Pp. 215. Balt.: Williams & Wilkins, 1948. Price, $3.50.

THIS edition of the first major book in psychiatry to emphasize the physical over the purely psychic approach has an excellent new chapter on epilepsy by Denis Hill. The techniques and appraisals of insulin and electric shock and other physical methods are brought well up to date in the 45 additional pages this edition contains. An excellent clinical book. J. S.